Imperial College London

STUDY PROTOCOL

DTP3

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Treating Multiple Myeloma and Diffuse Large B Cell Lymphoma by Targeting the NF-κB Pathway with the First-in-Class GADD45β/MKK7 Inhibitor, DTP3

Phase I/IIa Study of DTP3 in Patients With Advanced Multiple Myeloma or Diffuse Large B-cell Lymphoma

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Revision History:

Version	Date	Reason For Change
1.0	06-Sep-2021	Initial DTP3 Protocol
1.1	11-Nov-2021	Updates to Causality section 6.2 and contraception advice
1.2	26-Jan-2022	Updated Trial Assessments Table
1.3	14- Jun2022	update on inclusion criteria #4 and exclusion criteria #14 section 4.2.2
2.0	18-Oct-2022	Update to contact details on page 3 and safety contact reporting contacts on page 41; SAE reporting update with details of SAE paper form reporting; Correction of an error within the Schedule of Assessments relating to frequency of visits (expansion phase) for 12-lead ECG, BP and PR to match protocol wording; Change to the timeframes for EOS visit; Added minimum washout period post DTP3 treatment; Clarification of timepoints for survival status and disease progression once participant stops attending the hospital.
3.0	17-Jan-2023	Clarification of eligibility criteria; Contact details update; SoA escalation phase (cycle 3) error corrected
4.0	12-Dec-2023	Increase in dose-level for the dose escalation stage, changes in the proposed timelines to reflect this, clarification of cytogenetic risk in MM patients, clarification on the time windows for study procedures. Change to PD sample schedule and updates to schedule of assessment. Additional myeloma blood samples to be taken C1D1. Change to trial duration during dose escalation phase.

Protocol authorised by:

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Sponsor

Imperial College London is the research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Research Governance and Integrity at:

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Funder

The trial is being funded by the Medical Research Council, through the Developmental Pathway Funding Scheme (DPFS)/Biomedical Catalyst Scheme.

This protocol describes the **Phase I/IIa Study of DTP3 in Patients With Advanced MM and DLBCL** and provides information about procedures for entering patients. The protocol should not be used as a guide for the treatment of patients outside of this trial; every care has been taken in the drafting of this protocol, but corrections or amendments may be necessary from time to time as new relevant information emerges. These will be circulated to the investigators in the study, but centres entering patients for the first time are advised to contact the Trial Manager to confirm they have the most recent protocol version.

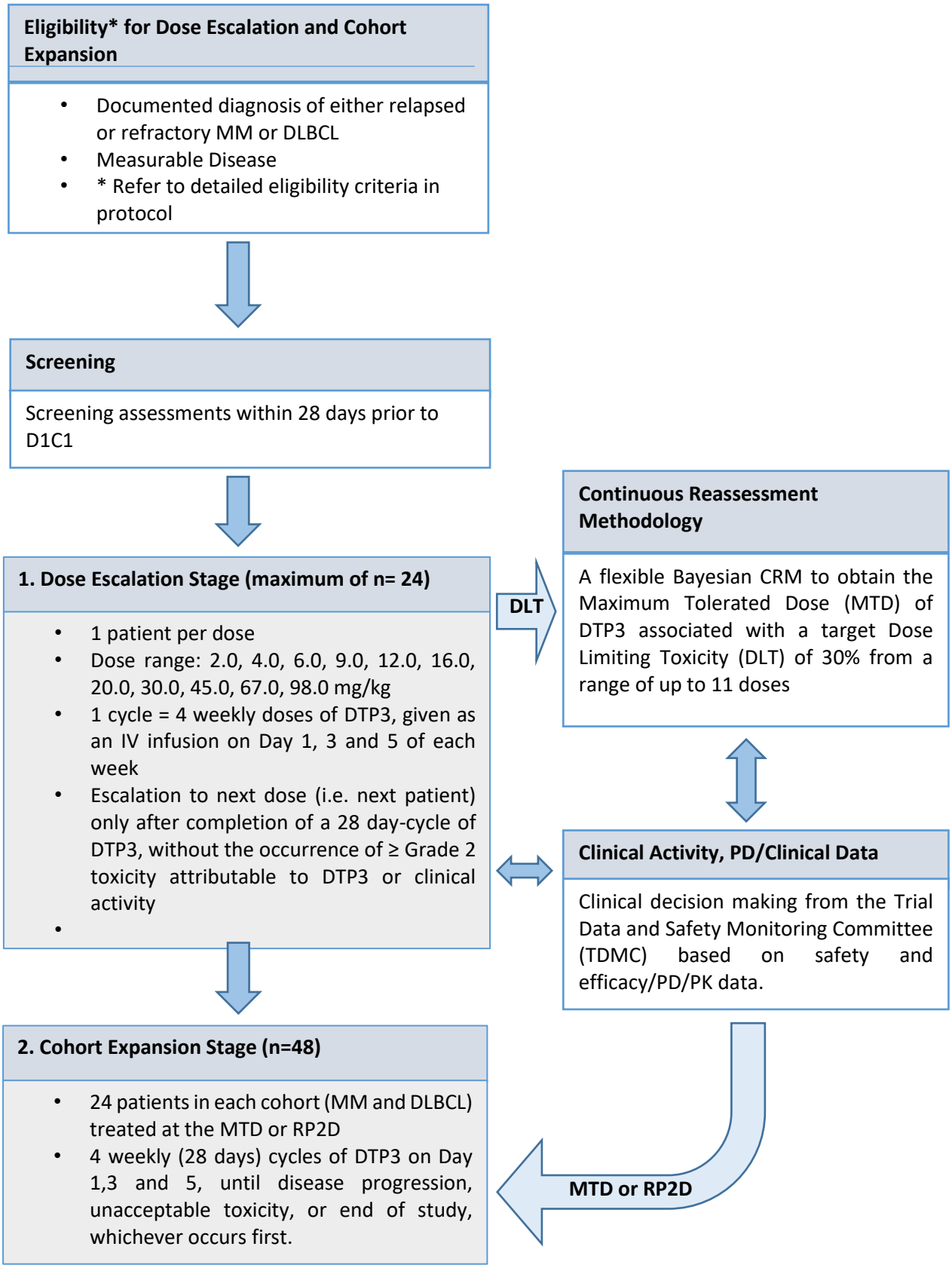
Issues relating to this trial should be referred, in the first instance, to the Trial Manager. This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. The trial will be conducted in compliance with the protocol, the Data Protection Act, and other regulatory requirements, as appropriate.

GLOSSARY OF ABBREVIATIONS

ABC	Activated B-cell like
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ASCT	Autologous Stem Cell Transplant
AUC	Area Under the Plasma Concentration Time Curve
AUC_{0-24}	Area Under Curve 0-24 Hours
$AUC_{0-\infty}$	Area Under Curve 0-Infinity
AV	Atrioventricular
AR	Adverse Reaction
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone
CNS	Central Nervous System
Con Meds	Concomitant Medications
C_{max}	Maximum Drug Plasma Concentration After Administration
CR	Complete Response
CRM	Continuous Reassessment Methodology
CRP	C-Reactive Protein
CTCAE	NCI Common Terminology Criteria for Adverse Events
DLBCL	Diffuse Large B-cell Lymphoma
DLT	Dose Limiting Toxicity
DTP3	D-Tripeptide 3
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ERK	Extracellular-Signal-Regulated Kinases
ESR	Erythrocyte Sedimentation Rate
FBC	Full blood count
GADD45β	Growth Arrest and DNA-Damage-inducible beta
GCB	Germinal Centre B-cell like
GCP	Good Clinical Practise
Hb	Haemoglobin
Hr	hours
TDSMC	Internal Data and Safety Committee
IMiD	Immunomodulatory Drug
IMP	Investigational Medicinal Product
IMWG	International Myeloma Working Group
IMWG-URC	IMWG-Uniform Response Criteria for Multiple Myeloma
INR	International Normalized Ratio
ISS	International Staging System
I.V.	Intravenous OR Intravenously

JNK	c-Jun N-Terminal Kinase
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
Min	minutes
MM	Multiple Myeloma
Msec	milliseconds
MTD	Maximum Tolerated Dose
NoAEL	No adverse effect level
NF-□B	Nuclear Factor Kappa- light-chain-enhancer of activated B cells
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral blood mononuclear cells
PC	Plasma Cell
PCI	Packaging Coordinators Inc
PD	Pharmacodynamics
PI	Principal Investigator
PFS	Progression Free Survival
PK	Pharmacokinetics
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Protein, and Skin Changes
PR	Partial Response
PT	Prothrombin Time
QTc	Corrected QT Interval
QWBA	Quantitative Whole Body Autoradiography
REC	Research Ethics Committee
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
Sec	seconds
sFLC	Serum Free Light Chain
SP	Safety-Evaluable Population
SPEP	Serum Protein Electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Half-Life Time Required for the Concentration of the Drug to Reach Half of Its Original Value
T_{max}	Time at Which the C_{max} is Observed
TMG	Trial Management Group
TK	Toxicokinetics
ULN	Upper Limit of Normal
UPEP	Urine Protein Electrophoresis
V_d	Volume of Distribution
V_{ss}	Volume of Distribution at Steady State
VGPR	Very Good Partial Response

TRIAL SCHEMATIC



STUDY SUMMARY

Title

Treating Multiple Myeloma and Diffuse Large B Cell Lymphoma by Targeting the NF-κB Pathway with the First-in-Class GADD45β/MKK7 Inhibitor, DTP3

Design

Phase I/IIa multi-centre open label dose escalation and cohort expansion study.

To assess the preliminary clinical efficacy of DTP3 in patients with relapsed or refractory multiple myeloma or diffuse large b-cell lymphoma

Objectives

Primary Objectives

- To select an optimal dose of DTP3 for further clinical evaluation [Recommended Phase 2 Dose (RP2D)] in patients with relapsed or refractory multiple myeloma or diffuse large B-cell lymphoma
- To assess the preliminary clinical efficacy of DTP3 in patients with relapsed or refractory multiple myeloma or diffuse large b-cell lymphoma

Secondary Objectives

- To assess the Dose Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD) of DTP3
- To assess the safety and tolerability of DTP3 in patients with relapsed or refractory multiple myeloma or diffuse large B-cell lymphoma
- To assess the pharmacokinetics of DTP3 in patients with relapsed or refractory multiple myeloma or diffuse large B-cell lymphoma
- To assess the pharmacodynamic activity of DTP3 in patients with relapsed or refractory multiple myeloma or diffuse large B-cell lymphoma
- To correlate GADD45β expression with pharmacodynamic and clinical response in patients with relapsed or refractory multiple myeloma or diffuse large B-cell lymphoma

Endpoints

Primary Endpoints

- Incidence, nature, and severity of all AEs, SAEs and DLTs
- Overall Response Rate (ORR)
    - **MM**: best overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR) or partial response (PR)
    - **DLBCL**: best overall response of PR or CR

Secondary Endpoints

- Changes in laboratory parameters, ECGs, vital signs
- Extent of exposure to DTP3
- PK parameters

- PD biomarkers of pathway-specific response
- Correlation of GADD45 expression with pharmacodynamic and clinical response
- Relative reduction in levels of M protein and free light chains [MM only]
- Clinical Benefit Rate
    - **MM**: minimal response (MR) or better
    - **DLBCL**: CR plus PR plus stable disease (SD)
- Time to Response (TTR)
- Duration of Response (DOR)
- Progression Free Survival (PFS)
- Event Free Survival (EFS)
- Overall Survival (OS)

Outcome measures

Toxicity and Tolerability

- AEs (CTCAE V5.0) will be assessed at each clinic visit and other assessments, including laboratory parameters, ECGs, vital signs will be assessed at designated intervals during each cycle of treatment

Pharmacokinetics

- PK of DTP3 will be examined on Day 1, Day 3 and Day 5 of Cycle 1
- Derived PK parameters will include: C_{max}, T_{max}, $t_{1/2}$, AUC $_{0\text{-}t}$, AUC $_{0\text{-}\infty}$, Vd, Vss

DTP3 Exposure

- Relative DTP3 dose intensity will be calculated for each patient and presented descriptively

Pharmacodynamics

- Mandatory samples (unless technically not possible) for pharmacodynamic (PD) assessment will be taken as follows:
    - At **screening** (within 28 days prior to DTP3 treatment)
    - **24 hours** (range 18-36 hr) after the **fourth dose** of DTP3 treatment (Cycle 1, Week 2, Day 2)
- Tissue will be collected as follows on each occasion for PD, genetic and biomarker assessment and sent in their entirety to the Hammersmith site (Prof Guido Franzoso's lab):
    - MM: 50 mL of blood and 10 mL of bone marrow aspirate
    - DLBCL: 50mL of blood and a tumour biopsy (18G core), if accessible.
- Pharmacodynamic (PD) markers will include:
    - phospho-JNK, and phospho-ERK (negative control)
    - cleaved caspase 3
    - propidium iodide nuclear staining

- propidium iodide permeability assay/annexin V

- Additional PD markers may be assessed in already collected blood samples and bone marrow (MM) or tumour biopsy samples (DLBCL), as further understanding of the mechanistic pathway of DTP3 is elucidated through ongoing non-clinical pharmacology studies.

Efficacy

- Response will be evaluated using IMWG 2016 (MM) and Lugano Criteria 2014 (DLBCL). MM disease evaluation will occur **4 weekly** and DLBCL imaging evaluation will occur **8 weekly.**

Study Population

This is a multi-centre study involving seven centres. Up to 37 DLT evaluable patients with multiple myeloma or diffuse large B-cell lymphoma will be entered into an initial dose escalation stage. A DLT evaluable, patient must have received at least 10 of the 12 scheduled Cycle 1 doses of DTP3 (unless a DLT prevented further DTP3 dosing). Subsequently at least 24 response-evaluable patients with multiple myeloma and at least 24 response evaluable patients with diffuse large B-cell lymphoma will be entered into an open label dose expansion stage. A response evaluable patient is defined as one who has completed at least one response assessment after at least two cycles of DTP3 or has documented disease progression at an earlier time point.

During the dose escalation stage, non-DLT evaluable patients will be replaced.

During the dose expansion stage, non-response evaluable patients may be replaced after discussion with the medical monitor (up to a study maximum of 85 patients).

Trial Duration

It will take a maximum of 32 months to conduct the dose escalation stage of the trial which will lead to a RP2D and a further 20 months to complete the dose expansion phase. Recruitment is expected to take approximately 15 months within the subsequent dose expansion stage. The last efficacy event will occur no more than 6 months after the last patient is recruited. The time from first patient recruited to preliminary efficacy evaluation will be approximately 44 months.

Eligibility

Disease specific inclusion criteria [MM]

1. Documented diagnosis of multiple myeloma (IMWG 2014 criteria)
2. Any R-ISS stage
3. Measurable disease as determined by at least one of:
    - Serum M-protein ≥ 500 mg/dL
    - Urine M-protein ≥ 200 mg/24 hour
    - Involved serum free light chain (sFLC) level ≥10 mg/dL, if serum sFLC ratio is abnormal.
4. Has previously been treated with an IMiD, a proteasome inhibitor and an anti-CD38 antibody. *Patients who have previously received only two categories of prior therapy may still be eligible, after discussion with the medical monitor, provided that the reason for omission of the third category was either unavailability as a standard of care regimen or medical contraindication.*
5. Previous treatment with at least 2 prior regimens

6. Relapsed (after most recent regimen) or refractory disease [refractory defined as either best response of progression on previous regimen or progression within 6 months of achieving PR (or better) on previous regimen]
7. Requires active therapeutic intervention (in the judgement of the investigator)
8. Not currently a candidate for stem cell transplantation or CAR T-cell therapy

Disease specific inclusion criteria [DLBCL]

9. Documented diagnosis of DLBCL [WHO 2016 criteria]
    - Diffuse large B-cell lymphoma – *de novo* or transformed (from follicular lymphoma only)
    - High-grade B-cell lymphoma (MYC with BCL2 and/or BCL6); High-grade B-cell lymphoma (NOS)
    - Primary mediastinal B-cell lymphoma
10. Non-GCB by local IHC [Dose Expansion Only]
11. Measurable disease as determined by:
    - CT (or MRI) documentation of 2 or more clearly demarcated lesions/nodes with a long axis > 1.5 cm and short axis > 1.0 cm or 1 clearly demarcated lesion/node with a long axis > 2.0 cm and short axis ≥ 1.0 cm **AND** baseline FDG-PET scans must demonstrate positive lesion compatibility with CT (or MRI) defined anatomical tumour sites.
12. No available standard of care therapeutic regimens in the opinion of the investigator
13. Relapsed (after most recent regimen) or refractory disease [refractory defined as either best response of progression on previous regimen or progression within 6 months of achieving PR (or better) on previous regimen]
14. Requires active therapeutic intervention (in the judgement of the investigator)
15. Not currently a candidate for stem cell transplantation or CAR T-cell therapy

General inclusion criteria:

16. Adequate hematologic function:
    - ANC ≥ 1 x 10^9/L (no restriction on prior growth factor support)
    - Platelet count ≥50 x 10^9/L (**no** platelet transfusions permitted in 7 last days prior to assessment). Platelet counts of <50 x 10^9/L may be considered, on a case-by-case basis, for patients with significant malignant bone marrow involvement, after discussion with the medical monitor
    - Hb ≥80 g/L (**no** RBC transfusions permitted in 7 last days prior to assessment)
    - aPTT and PT within institutional normal range (unless patient is on full-dose warfarin, in which case INR within normal institutional therapeutic range is acceptable). Values outside this normal range may still be considered on a case-by-case basis, if the result is clinically insignificant, after discussion with the medical monitor.
17. No evidence of bleeding diathesis or coagulopathy
18. Adequate laboratory biochemical function:
    - Serum creatinine ≤ 1.5 x ULN **OR** creatinine clearance ≥ 30 mL/min (Cockcroft-Gault calculation)
    - Bilirubin level < 1.5 X ULN.

- AST and ALT < 2.5 X ULN

19. ECOG performance status 0-2
20. Age >16 years
21. Written informed consent prior to admission into the study

Exclusion Criteria

1. Primary or secondary CNS lymphoma
2. T-cell rich B-cell lymphoma
3. Plasma cell leukaemia
4. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
5. Primary amyloidosis
6. Clinically significant (in the opinion of the investigator) cardiovascular disease, such as:
    - History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty/stenting/bypass grafting within the past 6 months prior to the date of consent
    - Class III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
    - Severe cardiac arrhythmia requiring medication or severe conduction abnormalities.
    - Poorly controlled hypertension (resting diastolic blood pressure >100 mmHg)
    - Clinically significant valvular disease, cardiomegaly, ventricular hypertrophy, or cardiomyopathy, QTc prolongation [defined as a QTc interval >450 msec (males) or >470 msec (females)] or other significant ECG abnormalities including 2nd degree (type II) or 3rd degree AV block or bradycardia (ventricular rate <50 beats/min)
7. Clinically significant (in the opinion of the investigator) cerebrovascular disorders or vascular dementia
8. Clinically significant (in the opinion of the investigator) intercurrent medical or psychiatric illness, including serious active infection
9. Significant neuropathy (Grade 3, Grade 4, or Grade 2 with pain)
10. Concurrent treatment with other experimental drugs
11. A daily requirement for prednisone at a dose of >10 mg/day (or steroid equivalent) at time of starting the first dose of study drug. Higher doses are permitted for primary disease symptomatic control during the screening period, after discussion with the medical monitor, but this must have been tapered to a dose of ≤10mg/day by the time treatment with DTP3 starts
12. Stem cell transplant (autologous/allogeneic) or CAR T-cell regimen within 12 weeks of the date of consent
13. Participation in another clinical trial with any investigational drug within 28 days prior to the date of consent
14. Prior (non-experimental) MM or DLBCL therapy within 28 days of first dose of DTP3. Concomitant bisphosphonate therapy is permitted.
15. Prior radiotherapy within 28 days of the date of consent. Localised palliative radiation therapy to a single site for symptomatic control is acceptable within this period.
16. Anticipated need for concurrent radiotherapy during the study
17. Past or current history of other neoplasms, except for
    - Curatively treated non-melanoma skin cancer

- Adequately treated in situ carcinoma of the cervix
- Prostate adenocarcinoma with documented PSA value of <0.1 ng/mL within six weeks of the date of consent
- Other cancer curatively treated and with no evidence of disease for at least 3 years before the date of consent.

18. Known HIV infection.
19. Active hepatitis C virus (HCV) or hepatitis B virus (HBV). Patients who are positive for hepatitis B core antibody, hepatitis B surface antigen or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result.
20. Ability to become pregnant (or already pregnant or lactating). However, those female patients who have a negative serum or urine pregnancy test before enrolment and agree to use two highly effective forms of contraception: i) oral, injected or implanted hormonal contraception [resulting in the inhibition of ovulation] and condom, ii) have an intra-uterine device and condom, iii) vasectomised partner [provided that the vasectomised partner is the only sexual partner of a woman of child bearing potential and that the vasectomised partner has received medical confirmation of surgical success or iv) complete sexual abstinence [sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse: periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable] during the trial and for 6 months after the last dose of DTP3 are considered eligible. Where age appropriate, female patients must be given advice on potential germ cell donation and cryopreservation.
21. Male patients with partners of child-bearing potential [unless they agree to take measures not to father children by using one form of highly effective contraception (condom plus spermicide) during the trial and for 90 days after the last date of DTP3]. Where age appropriate, male patients must be given advice on potential germ cell donation and cryopreservation, Men with pregnant or lactating partners should be advised to use barrier method contraception (for example, condom plus spermicidal gel) to prevent exposure to the foetus or neonate.

Treatment

Patients will be administered DTP3 intravenously (i.v.), given as a one hr infusion three times per week (with an inter-dose interval of a minimum of 40 hr and a maximum of 72 hr) in continual 4-week cycles until disease progression, unacceptable (drug related) toxicity or study termination, whichever occurs first.

Should a patient achieve a CR (DLBCL) or ≥PR (MM) of at least 12 weeks duration, the TDSMC will review all available data for that patient (AEs, clinical efficacy, PK, PD, DTP3 dose intensity) and make a recommendation to the relevant investigator about whether to reduce the weekly frequency of DTP3 administration.

In the dose escalation stage, the following maximum potential range of DTP3 dose levels will be examined:

2.0, 4.0, 6.0, 9.0, 12.0, 16.0, 20.0, 30.0, 45.0, 67.0, 98.0 mg/kg

The starting dose of 2.0 mg/kg is the highest dose tested in an earlier clinical trial, which showed no significant AEs at any dose level.

The dose escalation will employ a flexible Bayesian Continuous Reassessment Methodology (CRM) to obtain the Maximum Tolerated Dose (MTD) of DTP3 associated with a target Dose Limiting Toxicity (DLT) of 30% from a range of up to 11 doses.

A TDSMC will review, on an ongoing basis, all available safety and efficacy/PD/PK data.

The first patient will be given a starting dose of 2 mg/kg. If no DLT occurs, the next patient will only be dosed at the next higher dose after the preceding patient has completed 4 weeks of treatment and the TDSMC has reviewed the safety data to decide whether to proceed to the next dose level.

Dose escalation will occur with one patient per dose level cohort. In the absence of a DLT occurring within the first 28 days after Day 1 of DTP3 administration escalation to the next scheduled dose level will occur following review of all relevant data by the TDMC.

If a DLT is observed at any dose level, dose escalation will revert to at least 3 patients per cohort for the current dose level and for all subsequent dose levels (to further assess safety. The TDSMC may also recommend increasing the number of patients at specific dose levels, to obtain further information to aid dose selection, or evaluation of doses which are intermediate to the pre-specified dose levels in order to further characterise the relationship between dose level and emergent toxicities.

Once a DLT has been observed, the CRM model will commence estimating the DLT rate at each dose level and recommend the next best dose level with an estimated DLT rate closest to 30% for subsequent patients, using all the accrued DLT data at all doses. An empiric dose-toxicity model $F(\chi,\beta)=\chi^{\exp(\beta)}$, $0<\chi<1$ will be used, where the slope parameter β is assumed to follow a normal distribution with prior mean 0 and a pre-specified prior variance of 1.

At any time during the dose escalation stage, the TDSMC may recommend initiation of one or both expansion cohorts (MM and/or DLBCL) if it considers that a sufficiently strong efficacy signal and acceptable safety profile has been confirmed at that dose level (which will then be designated the RP2D level).

The **same** RP2D will be defined for each of the two expansion cohorts.

A minimum of six [DLBCL and/or MM] patients will be treated for at least 28 days with the RP2D dose level [with review of all relevant clinical data by the TDSMC] prior to initiation of the dose expansion stage.

In this situation the TDSMC will decide whether the dose escalation stage should continue in parallel with the expansion stage, to further define the safety and tolerability of DTP3 up to a maximum tolerated dose, if this has not yet been determined.

If the TDSMC does not recommend an RP2D level prior to identification of the MTD, the committee will convene following determination of an MTD to review all available safety, efficacy, PK and PD data and formally recommend an RP2D level to take into the dose expansion stage. The **same** RP2D level will be evaluated in both the MM and DLBCL cohorts.

During the dose expansion stage, the TDSMC will review ongoing safety data with a frequency no less than every seven patients (across both cohorts) who have been treated for at least 8 weeks of DTP3. (*i.e.* minimum of 2 cycles of treatment). Dose delays due to DTP3 related toxicity are included as part of the 8 week period [*i.e* if there is a dose delay during the 8 week period, a patient will still be reviewed for safety even though they may not have received two complete cycles of DTP3].

DLTs

DLTs are defined as the following events occurring within the first 28 days of dosing with DTP3, *i.e.* up to the end of Cycle 1, corresponding to up to 12 doses of DTP3 and which are considered to be at least **probably** related to DTP3:

- Any Grade 4 non-haematological adverse event not resolving to at least Grade 3 within 48 hrs
- Any Grade 3 non-haematological event not resolving to at least Grade 2 within 14 days

  Excluding:

  - Grade 3 nausea
  - Grade 3 anorexia
  - Grade 3 or 4 vomiting in patients who have not received optimal treatment with anti-emetics
  - Grade 3 or 4 diarrhoea in patients who have not received optimal treatment with anti-diarrhoeal agents
  - Grade 3 fatigue
  - ≥Grade 3 laboratory abnormalities considered by the investigator to be **not** clinically relevant
  - ≥3 Grade 3 laboratory TLS if corrected by institutional management
- Grade 4 neutropenia for more than 7 days despite optimal growth factor support
- Grade 4 thrombocytopenia for more than 14 days (with or without platelet support) or associated with active bleeding at any time
- Any other toxicity judged by the TDMSC to be dose limiting in nature
- Death

To be **DLT evaluable**, a patient must have received at least 10 of the 12 scheduled doses of DTP3 (unless a DLT prevented further DTP3 dosing). Non-evaluable patients will be replaced for DLT estimation purposes but may remain in the study.

Dose Modification

Dose Escalation Stage Only

- No dose reductions are permitted for any patient during the DLT evaluation period [Cycle1 of DTP3].
- Patients experiencing a DLT may remain in the study at the originally assigned dose of DTP3 or a lower dose level according to investigator judgement.
- Patients initially entered into the study at a DTP3 dose level lower than the one currently being evaluated may increase their DTP3 dose level [provided they have not experienced a DLT during the DLT evaluation period] by one dose level increment per cycle, at the end of each cycle of treatment, at the discretion of the investigator, provided the DTP3 dose remains at least one level below the highest dose level currently being evaluated.

Dose Escalation and Expansion Stage

- Up to **three** dose level reductions are permitted in the event of DTP3 related toxicity, at the discretion of the investigator.
- During the **dose escalation stage**, [for patients who have completed the initial DLT evaluation period] each dose reduction should be to the immediately preceding dose level specified in the

DTP3 dose level escalation range [*e.g.*20mg/kg reduced to 16mg/kg; 16mg/kg reduced to 12mg/kg *etc*].

- For the **dose expansion stage**, the TDSMC will specify a dose reduction algorithm at the time the RP2D level is determined, taking account of the actual RP2D level and the pattern of toxicities seen at lower dose levels during the dose escalation stage.
- Dose reductions are permitted for the following toxicities if they are considered clinically relevant by the investigator:
    - Any Grade 4 adverse event not resolving to at least Grade 3 within 48 hr
    - Any Grade 3 adverse event not resolving to at least Grade 2 within 14 days
    - Any dose delay greater than 7 days
- If a dose level is reduced, it may be increased again (to the immediately preceding dose level) , at the discretion of the investigator, if there is complete resolution of the original toxicity leading to the dose reduction.
- Dose delays of up to 14 days are permitted for the resolution of DTP3 related toxicity. Patients requiring a dose delay greater than 14 days should be withdrawn from the study. Dose delays of greater than 14 days for reasons other than DTP3 related toxicity (*e.g.* logistical ones) must be discussed with and approved by the medical monitor.

Study Procedures

Study Assessments and relevant timings are detailed in the protocol. If the protocol specified procedures and/or timings cannot be adhered to, due to any prevailing COVID19 restrictions, these will **not** be considered protocol deviations but will be documented accordingly.

Analysis Plan

Safety Endpoints

- The MTD will be defined as the dose with an estimated DLT rate closest to the 30% target DLT rate.
- The estimated DLT rate of the MTD and RP2D with 90% probability intervals will be reported.
- Toxicity data (AE, SAE, DLT) will be summarised by dose.
- Safety will be monitored in patients treated with at least one dose of DTP3 until end of follow-up.

Efficacy Endpoints

- Efficacy data will be summarised by dose.
- Clinical response will primarily be evaluated using **overall response rate** (ORR), separately for the MM and DLBCL cohorts, defined by the International Myeloma Working Group 2016 (MM) or Lugano 2014 (DLBCL) criteria respectively.
- Patients who are dosed at the RP2D level in the dose escalation stage will contribute to the expansion stage [DLBCL patients must meet the eligibility criteria for the expansion stage (*i.e* must have a non-GCB gene signature)]

- Time-to-event outcomes for efficacy [time to response, duration of response, progression free survival, event free survival and overall survival] will be analysed using the Kaplan-Meier method.

Pharmacokinetic Endpoints

Data will be presented descriptively by dose level.

DTP3 Exposure

Relative DTP3 dose intensity (delivered dose *versus* intended dose) will be calculated for each patient and presented descriptively by dose level.

Pharmacodynamic Endpoints

Data will be presented descriptively by dose level.

Sample Size

A sample size of 24 (per cohort) provides a one-sided 90% lower-limit confidence interval of at least 27.7% when the observed response rate is ≥41.7% using the Exact Clopper-Pearson interval method. This exceeds the minimum response rate of 25% required to justify further testing for each cohort.

1. INTRODUCTION

1.1 Background

The study is intended to evaluate DTP3 as a novel modulator of the NF-κB pathway in patients with relapsed/refractory multiple myeloma (MM) or diffuse large B-cell lymphoma (DLBCL), both of which represent intractable clinical settings with exceptionally poor longer-term outcomes and hence a pressing need for new therapeutic strategies.

The management of newly diagnosed MM is primarily determined by both patient prognostic parameters and potential eligibility for eventual high dose chemotherapy followed by autologous stem cell transplant (ASCT).[1,2,3,4,5]

Current treatment approaches for both front-line and relapsed/refractory disease include immunomodulatory (IMiD) agents (thalidomide, lenalidomide and pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, ixazomib), HDAC inhibitors such as panobinostat, anti-CD38 antibodies (*e.g*. daratumumab, isatuximab) and various combinations of alkylating agents, corticosteroids and anthracyclines such as doxorubicin. More recently, encouraging data with immunotherapy approaches [especially adoptive cellular regimens] are beginning to emerge.[6,7,8,9,10,11]

Whilst the overall survival of patients with multiple myeloma is improving in general and successful ASCT can further increase survival by an additional eighteen months or so, myeloma remains an incurable disease, with the vast majority of patients eventually relapsing and becoming resistant to therapy.

The progression free survival and overall survival in patients with relapsed myeloma no longer responsive to IMiDs, proteosome inhibitors and anti-CD38 directed therapy [*i.e* the population for this study] is extremely poor, with median times of approximately 5 and 10 months, respectively.[12,13,14,15,16,17,18] Only about a third of these patients will achieve a clinically useful response with currently available therapeutic strategies, which largely include experimental approaches and various re-permutations of drugs used in earlier stages of the disease. Furthermore, the remission duration in relapsed myeloma progressively decreases with each successive regimen.[19,20,21]

Whilst the majority of patients with DLBCL can effectively be cured with front-line immuno-chemotherapy regimens [largely consisting of anthracycline combination chemotherapy and an anti-CD20 antibody] over a third will either be refractory to therapy or relapse after an initial response.[22,23,24] The prognosis in this population remains poor, with typical reinduction regimens consisting of combination chemotherapy (plus/minus rituximab) consolidated with autologous stem cell transplant (in selected cases) antibody drug conjugates and bispecific antibodies.[25,26,27,28]

A minority of relapsed/refractory patients are suitable for treatment with anti-CD19 CAR T-cell regimens. Although a small proportion of these may derive long term disease remission (potentially consistent with a curative outcome) most patients experience either no response or short-lived remissions.[29,30,31]

The outcome for patients failing to respond to an initial salvage regimen is poor, with a median overall survival of about 6 months.[33,34,35,36] Likewise for those patients who are not suitable for intensive reinduction therapies there is an urgent need to improve outcomes.

Overall, therefore, the relapsed/refractory MM and DLBCL settings of the current study represent major unmet medical challenges in desperate need of novel therapeutic strategies capable of achieving durable responses in patient populations devoid of standard of care management regimens.

1.2 Rationale for Current Study

The NF-κB pathway has been extensively implicated in the pathogenesis of MM, with constitutive NF-κB activity being observed in virtually all cases. NF-κB activity is also a major contributory factor in the development of chemo-resistance in patients with advanced disease. Similarly, virtually all cases of the activated B cell (ABC/ non-GCB) subtype of DLBCL and primary mediastinal B-cell lymphoma (PMBCL) and a minority of cases of the germinal centre B cell (GCB) subtype of DLBCL, display an aberrant activation of the NF-κB pathway and depend on this aberrant NF-κB activity for malignant cell survival and pathogenesis.[37,41,42]

Despite the clear causative role of the NF-κB pathway in MM and DLBCL pathogenesis, NF-κB-targeting strategies have, to date, translated into only limited clinical efficacy in the management of MM and DLBCL patients.[40,41,42] This is because indiscriminate targeting of the proteasome/NF-κB axis results in extensive and dose-limiting toxicity, thus preventing potentially effective therapies from being used clinically at dose levels which could achieve long-lasting clinical benefit. This limitation emphasises the need for a more specific, and therefore more effective, therapeutic approach.

The interaction between the NF-κB-regulated anti-apoptotic factor, GADD45β, and the JNK kinase, MKK7, has been identified as a pathogenically critical and cancer cell-restricted survival module downstream of NF-κB and a novel therapeutic target in MM and, more recently DLBCL. DTP3 (a D-tripeptide inhibitor of the GADD45β/MKK7 complex), effectively kills MM and DLBCL cells by inducing MKK7/JNK-dependent apoptosis and, importantly, is not toxic to normal tissues.[43,44,48]

In vitro studies in MM serial cell lines and primary MM *ex vivo* patient cells demonstrated a clear induction of cell death by apoptosis at doses of DTP3 in the low nanomolar to low micromolar **Error! Reference source not found.** Treated cells were also analysed by western blot and flow cytometry, with results showing that a single administration of DTP3 was effective in inducing JNK activation and that this activity was maintained at least up to 24 hr but lost by 48 hrs. Repeated administration of DTP3 resulted in greater apoptosis as compared to single treatment. Similarly, JNK and caspase 3 (measures of pathway engagement and apoptosis) were strongly activated by multiple administrations of DTP3. Notably, DTP3 retained full therapeutic efficacy in MM cells that are resistant to most conventional MM treatments, which could be of major clinical significance, as nearly all patients will eventually relapse and/or develop drug resistance[43,44].

The analysis of DLBCL datasets from patients demonstrated that GADD45β expression correlated with the NF-κB target gene signature and shorter overall survival (OS) following treatment with CHOP-like or Rituximab-CHOP-like therapy. Studies in DLBCL cell lines demonstrated that GADD45β is preferentially (albeit not exclusively) expressed in ABC (non-GCB) relative to GCB cell lines. In agreement with these data*, in vitro* studies of DTP3 in DLBCL serial cell lines and primary *ex vivo* DLBCL patient cells demonstrated a selective induction of JNK activation and apoptosis in most cells exhibiting elevated GADD454β expression, when analysed by western blot or flow cytometry. These effects resulted in a clear induction of cell death at doses of DTP3 in the nanomolar to low micromolar range. Notably, DTP3 retained full therapeutic efficacy in DLBCL cells resistant to ibrutinib and/or idelalisib, two drugs widely used for the treatment of DLBCL.

In vivo PD studies in a mouse MM xenograft model have determined that either continuous infusion (14.5 mg/kg/day) or daily i.v. bolus administration of DTP3 virtually eradicated or markedly reduced tumour volume *via* strong tumour-selective activation of JNK signalling and apoptosis. Subsequent studies of injected i.v. bolus administration of at least 10 mg/kg of DTP3 over a period of 2 weeks, either daily, every other day, or every 3 days, have shown tumour regression in a mouse MM xenograft model which supports the proposed dosing strategy in man.[48] Similarly, i.v. bolus administration of 30 mg/kg of DTP3 every other day produced a profound regression of ibrutinib- and idelalisib-resistant DLBCL in a mouse xenograft model, which supports the potential clinical utility of DTP3 in this indication.

During the first-in-human trial of DTP3 in patients with relapsed or refractory MM, three single-patient dose escalation cohorts were evaluated at dose levels of 0.5, 1 and 2 mg/kg, given as a 1-hr i.v. infusion 3 times/week (EudraCT: 2015-003459-23).[44] All enrolled patients had progressive disease and multiple lines of prior therapy. PD analysis of tissue samples from these MM patients demonstrated JNK phosphorylation (denoting therapeutic target engagement) and caspase-3 cleavage (a hallmark of apoptosis) in MM cells from two of the three patients upon DTP3 administration (but not at screening) while no such signals were detected in either B-cells or peripheral blood mononuclear cells (PBMCs) from the same patients, thus establishing clinical proof-of-mechanism for the mode of action of DTP3.[43,33]

In addition, PK and TK evaluation of DTP3 in both rat and dog have identified long plasma half-lives, which have been modelled into a predicted half-life of 17-22 hr in man. In line with these preclinical data, the PK profile of DTP3 in MM patients from the previous pilot study demonstrated the AUC proportionality of DTP3 to dose level, a relatively long human plasma half-life (10-14 hr), and no accumulation on repeated dosing.

In summary therefore, due to its cancer-selective target specificity, DTP3 represents an opportunity for substantial anti-MM and anti-DLBCL activity, without preclusive clinical toxicity, and therefore a potential benefit to patients.

1.3 Pharmacotoxicology and Pharmacokinetics

DTP3 has been evaluated against a broad panel of receptors, channels and enzymes to evaluate secondary PD effects.[44] Activity was demonstrated for only one receptor, namely the Sigma receptor (non-specific). The binding was only seen, however, at the relatively high concentration of 10 µM. In a follow up study DTP3 was found to have moderate antagonist activity for the Sigma receptor. These and other data suggest negligible off target activity of DTP3.

Safety pharmacology studies have demonstrated that DTP3 does not adversely affect the respiratory and central nervous system in rats when given i.v. at doses up to the maximum administered dose of 100 mg/kg. In the conscious telemetered dog, DTP3 had no adverse effects on the cardiovascular system at i.v. doses up to the maximum dose tested of 25 mg/kg. In an *in vitro* hERG assay the maximum concentration tested of DTP3 (150 µg/mL) resulted in less than a 10% inhibition of hERG assay tail current. The *in vitro* plasma protein binding of DTP3 is low (80% or less) in mouse rat, dog, and human.[44]

PK studies in mouse, rat and dog indicate that systemic exposure and maximum plasma concentrations increased with increasing dose of DTP3 and half-life was greater in preclinical animal species as follows: dog>rat>mouse. There was no evidence of a gender difference in PK parameters and V_d parameters indicated that DTP3 is distributed to tissues. This was confirmed in a QWBA study in the rat in which 15 mg/kg [^{14}C]-DTP3 was administered i.v. This study demonstrated that DTP3 was rapidly and extensively distributed to organs and tissues throughout the body. Notably however, radioactivity was not detected in the brain or spinal cord. The highest levels of radioactivity were observed in the urine, kidney, liver, and gall bladder.

In vitro, there was no significant metabolism of DTP3 in rat, dog or human hepatocytes. In an *in vivo* rat study, in which an i.v. dose of 15 mg/kg [^{14}C]-DTP3 was administered, there were no major metabolites identified in plasma, faeces or urine. Approximately 30% of the radioactivity was recovered in urine and 60% was recovered in faeces.

In the rat and dog 28 day repeat dose toxicity studies, no target organs of toxicity were identified. The maximum doses administered in these studies were based on clinical signs observed in prior dose ranging studies in each species. DTP3 was well tolerated in the rat, and the NOAEL in this species was

100 mg/kg/day. In the dog, DTP3 was also well tolerated, and the NOAEL was 50 mg/kg/day. Based on exposure in the mouse efficacy studies at 10 mg/kg, these NOAEL are 17 and 18 times the effective exposure for rat and dog respectively.

DTP3 was not mutagenic in a bacterial Ames assay, with or without metabolic activation.

Clinical PK was evaluated in the recent first-in-human trial involving 3 MM patients with progressive disease who had tried multiple lines of prior therapy.[43] PK evaluation of these three patients showed half-lives between 10 and 14 hours. Exposure increased with the dose, as expected, and there was no accumulation after repeated doses. C_{max} at 2mg/kg was around 5700 ng/ml and $AUC_{0\text{-}inf}$ around 15000 ng.h/ml, exposures clearly lower than the ones seen in animals (rats and dogs) at their NoAEL.

Overall, the PK and non-clinical safety profiles of DTP3 therefore support the evaluation of this agent in the late-stage treatment of patients with relapsed or refractory multiple myeloma or diffuse large B-cell lymphoma.

1.4 Justification of the DTP3 starting dose

For the purpose of deriving the original human starting dose for the clinical trial, the rat was considered the most sensitive species. This is based on the observation that, although low, protein binding is approximately 80% in the rat, compared to approximately 20% in man, and therefore reference to the rat NOAEL derives the most conservative human starting dose.

Allometrically scaled (*i.e.* divided by 6) the NOAEL in the rat of 100 mg/kg is a human dose equivalent of 16 mg/kg. This human dose equivalent was reduced by a factor of 4 to correct for the difference in protein binding to derive a dose of 4 mg/kg. A further safety factor (approximately 8) was applied to establish the human starting dose of 0.5 mg/kg.

The pharmacokinetic profile of DTP3 was assessed using the pooled pre-clinical data available from the mouse, rat and dog studies undertaken to date and selected pre-clinical datasets were then subjected to simple scaling methodology to predict the potential clearance of the compound in man. Based upon the lower of the two human clearance predictions (derived from the rat), the $AUC_{0\text{-}48}$ in man at the proposed clinical starting dose of 0.5 mg/kg, would be expected to be approximately 2300 ng.h/ml, i.e. between 12 and 31% of the unbound AUC achieved over a 48 h period following daily dosing to the dog and rat at the lowest dose levels used in the one month studies (10 and 8% if based on total concentrations).

The projected human exposure of 2300 ng.hr/mL at the original starting dose of 0.5 mg/kg compares to the exposure of 1029 ng.hr/mL at a minimally effective dose of 2.5 mg/kg in the mouse MM xenograft model. At the highest proposed clinical dose of 20 mg/kg, assuming dose proportionality, the $AUC_{0\text{-}48}$ in man would be expected to be approximately 92600 ng.h/ml *i.e*. between 59 and 225% of the unbound AUC achieved over a 48 h period in dog and rat at the highest-dose level in the two one month toxicology studies (50 and 55% if based on total concentrations).

Additionally, potential safety risks will be substantially mitigated as DTP3 will be administered i.v. 3 times per week by a 1 hr infusion compared to the pivotal toxicity studies, in which DTP3 was administered daily by a fast 10 min infusion. The maximum DTP3 plasma concentrations will therefore be significantly reduced, and the infusion may be terminated prematurely if this is considered necessary.

DTP3 has previously been evaluated in 3 multiple myeloma patients at dose levels up to 2.0 mg/kg with no significant safety concerns [a total of 14 AEs were recorded (13 mild and one moderate in severity) all of which were considered by the investigator to be either unrelated or unlikely related to DTP3]. Furthermore, 2/3 patients showed evidence of anticipated pharmacodynamic response to DTP3, with one patient recording a best response of stable disease whilst receiving study drug.

The currently proposed DTP3 starting dose of 2.0 mg/kg is therefore considered appropriate and justified by the totality of available pre-clinical and clinical data.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives

Primary Objectives

- To select an optimal dose of DTP3 for further clinical evaluation [Recommended Phase 2 Dose (RP2D)] in patients with relapsed or refractory multiple myeloma or diffuse large B-cell lymphoma
- To assess the preliminary clinical efficacy of DTP3 in patients with relapsed or refractory multiple myeloma or diffuse large b-cell lymphoma

Secondary Objectives

- To assess the Dose Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD) of DTP3
- To assess the safety and tolerability of DTP3 in patients with relapsed or refractory multiple myeloma or diffuse large B-cell lymphoma
- To assess the pharmacokinetics of DTP3 in patients with relapsed or refractory multiple myeloma or diffuse large B-cell lymphoma
- To assess the pharmacodynamic activity of DTP3 in patients with relapsed or refractory multiple myeloma or diffuse large B-cell lymphoma
- To correlate GADD45β expression with pharmacodynamic and clinical response in patients with relapsed or refractory multiple myeloma or diffuse large B-cell lymphoma

Endpoints

Primary Endpoints

- Incidence, nature, and severity of all AEs, SAEs and DLTs
- Overall Response Rate (ORR)
    - **MM**: best overall response of stringent complete response (sCR), complete response CR, very good partial response (VGPR) or partial response (PR)
    - **DLBCL**: best overall response of PR or CR

Secondary Endpoints

- Changes in laboratory parameters, ECGs, vital signs
- Extent of exposure to DTP3
- PK parameters
- PD biomarkers of pathway-specific response:
- Correlation of GADD45 expression with pharmacodynamic and clinical response
- Relative reduction in levels of M protein and free light chains [MM only]
- Clinical Benefit Rate
    - **MM**: minimal response (MR) or better
    - **DLBCL**: CR plus PR plus stable disease (SD)

- Time to Response TTR)
- Duration of Response (DOR)
- Progression Free Survival (PFS)
- Event Free Survival [time to death, disease progression or initiation of non-protocol anti-cancer therapy] (EFS)
- Overall Survival (OS)

3. STUDY DESIGN

This is a multi-centre Phase I/IIa dose escalation and subsequent cohort expansion study. Up to 37 DLT evaluable patients with multiple myeloma or diffuse large B-cell lymphoma will be entered into an initial dose escalation stage. A DLT evaluable, patient must have received at least 10 of the 12 scheduled Cycle 1 doses of DTP3 (unless a DLT prevented further DTP3 dosing). Subsequently at least 24 response evaluable patients with multiple myeloma and at least 24 response evaluable patients with diffuse large B-cell lymphoma will be entered into an open label dose expansion stage. A response evaluable patient is defined as one who has completed at least one response assessment after at least two cycles of DTP3, unless disease progression has been documented at earlier time point.

During the dose escalation stage, non-DLT evaluable patients will be replaced.

During the dose expansion stage, non-response evaluable patients may be replaced after discussion with the medical monitor.

It will take a maximum of 32 months to conduct the dose escalation stage of the trial which will lead to a RP2D, and a further 20 months to complete the dose expansion phase.

3.1 Study Outcome Measures

Toxicity and Tolerability

- AEs (CTCAE V5.0) will be assessed at each visit to the clinic, and other assessments, including laboratory parameters, ECGs, vital signs will be assessed at designated intervals during each cycle of treatment

Pharmacokinetics

- PK of DTP3 will be examined on Day 1, Day 3, and Day 5 of Cycle 1
- Derived PK parameters will include: C_{max}, T_{max}, $t_{1/2}$, AUC $_{0\text{-}t}$, AUC $_{0\text{-}\infty}$, Vd, Vss

DTP3 Exposure

- Relative DTP3 dose intensity (delivered dose *versus* intended dose) will be calculated for each patient and presented descriptively.

Pharmacodynamics

- Mandatory samples (unless technically not possible) for pharmacodynamic (PD) assessment will be taken as follows:
    - At **screening** (within 28 days prior to DTP3 treatment)
    - **24 hours** (range 18-36 hr) after the **fourth dose** of DTP3 treatment (Cycle 1, Week 2, Day 2),
- Tissue will be collected as follows on each occasion for PD, genetic and biomarker assessment and sent in their entirety to the Hammersmith site (Prof Guido Franzoso's lab):

- MM: 50 mL of blood and 10 mL of bone marrow aspirate
- DLBCL: 50mL of blood and a tumour biopsy (18G core), if accessible

- Pharmacodynamic (PD) markers will include:
  - phospho-JNK, and phospho-ERK (negative control)
  - cleaved caspase 3
  - propidium iodide nuclear staining
  - propidium iodide permeability assay / annexin V
- Additional PD markers may be assessed in already collected blood samples and bone marrow (MM) or tumour biopsy samples (DLBCL), as further understanding of the mechanistic pathway of DTP3 is elucidated through ongoing non-clinical pharmacology studies.

Efficacy

- Response will be evaluated using IMWG 2016 (MM) [(Appendix A)] and Lugano Criteria 2014 (DLBCL).[Appendix B] MM disease evaluation will occur **4 weekly** and DLBCL imaging evaluation will occur **8 weekly**

4. PARTICIPANT ENTRY

4.1 Screening Evaluations

At screening (*within 28 days* prior to the Dose 1 of Cycle 1 of DTP3) all patients will be assessed as follows:

- Written informed consent
- Medical history
- Disease specific history (MM/DLBCL)
- Concomitant medications
- Physical examination
- Vital signs [blood pressure, pulse rate and respiratory rate]
- Height and weight
- 12- lead ECG
- Urinalysis, full blood count, biochemistry panel, calculated creatinine clearance
- Coagulation testing (PT and aPTT)
- Pregnancy test (serum) where appropriate
- MM and DLBCL-specific assessments.

  MM -specific assessments will include:

  - Serum protein electrophoresis (SPEP), paraprotein quantification, serum immunofixation, serum immunoglobulin levels, and serum free light chain (sFLC), and 24-hr urine sample for urine protein electrophoresis (UPEP), and urine immunofixation

- FDG-PET/CT, whole body MRI, or whole-body low-dose CT according to local institutional clinical practice (unless already performed within last 8 weeks prior to the date of consent and results are available to the investigator)
- β-2 microglobulin level
- Bone marrow aspirate and biopsy sample will be sent for local determination of plasma cell count
- 50 mL of blood and 10 mL of bone marrow aspirate will be taken for PD, genetic and biomarker assessment and sent in their entirety to the Hammersmith site (Prof Guido Franzoso's lab)
- Cytogenetic abnormalities evaluation through FISH [for evaluation of translocations t(4;14), t(14;16), t(11;14), and t(14;20), deletion 17p, gain of 1q, loss of 1p, hyperdiploidy]

DLBCL-specific assessments will include:

- FDG-PET/CT scan (unless already performed within 28 days of date of consent and results are available to the investigator)
- Bone marrow aspirate and biopsy [for histological evaluation of DLBCL involvement]
- 50 mL of blood and a tumour biopsy (18G core), if accessible, will be taken for PD, genetic and biomarker assessment and sent in their entirety to the Hammersmith site (Prof Guido Franzoso's lab)

4.2 Eligibility Criteria

4.2.1 Inclusion Criteria:

Disease specific inclusion criteria:

Disease specific inclusion criteria [MM]

1. Documented diagnosis of multiple myeloma (IMWG 2014 criteria)[47,Appendix A]
2. Any R-ISS stage
3. Measurable disease as determined by at least one of:
   - Serum M-protein ≥ 500 mg/dL
   - Urine M-protein ≥ 200 mg/24 hour
   - Involved serum free light chain (sFLC) level ≥10 mg/dL, if serum sFLC ratio is abnormal
4. Has previously been treated with an IMiD, a proteasome inhibitor and an anti-CD38 antibody

Patients who have previously received only two categories of prior therapy may still be eligible, after discussion with the medical monitor, provided that the reason for omission of the third category was either unavailability as a standard of care regimen or medical contraindication.

5. Previous treatment with at least 2 prior regimens
6. Relapsed (after most recent regimen) or refractory disease [refractory defined as either best response of progression on previous regimen or progression within 6 months of achieving PR (or better) on previous regimen]
7. Requires active therapeutic intervention (in the judgement of the investigator)

8. Not currently a candidate for stem cell transplantation or CAR T-cell therapy

Disease specific inclusion criteria [DLBCL]

9. Documented diagnosis of DLBCL [WHO 2016 criteria[49,Appendix B]]
    - Diffuse large B-cell lymphoma – *de novo* or transformed (from follicular lymphoma only)
    - High-grade B-cell lymphoma (MYC with BCL2 and/or BCL6); High-grade B-cell lymphoma (NOS)
    - Primary mediastinal B cell lymphoma
10. Non-GCB by local IHC [Dose Expansion Only]
11. Measurable disease, as determined by:

    CT (or MRI) documentation of 2 or more clearly demarcated lesions/nodes with a long axis > 1.5 cm and short axis > 1.0 cm or 1 clearly demarcated lesion/node with a long axis > 2.0 cm and short axis ≥ 1.0 cm **AND** baseline FDG- PET scans must demonstrate positive lesion compatibility with CT (or MRI) defined anatomical tumour sites.
12. No available standard of care therapeutic regimens in the opinion of the investigator
13. Relapsed (after most recent regimen) or refractory disease [refractory defined as either best response of progression on previous regimen or progression within 6 months of achieving PR (or better) on previous regimen].
14. Require active therapeutic intervention (in the judgement of the investigator)
15. Not currently a candidate for stem cell transplantation or CAR T-cell therapy

General inclusion criteria:

16. Adequate hematologic function:
    - ANC ≥ 1 x 10^9/L (no restriction on prior growth factor support)
    - Platelet count ≥50 x 10^9/L (no platelet transfusions permitted in 7 last days prior to assessment) Platelet counts of <50 x 10^9/L may be considered, on a case-by-case basis, for patients with significant malignant bone marrow involvement, after discussion with the medical monitor
    - Hb ≥80 g/L (no RBC transfusions permitted in 7 last days prior to assessment)
    - aPTT and PT within institutional normal range (unless patient is on full-dose warfarin, in which case INR within normal institutional therapeutic range is acceptable). . Values outside this normal range may still be considered on a case-by-case basis, if the result is clinically insignificant, after discussion with the medical monitor.
17. No evidence of bleeding diathesis or coagulopathy
18. Adequate laboratory biochemical function:
    - Serum creatinine ≤ 1.5 x ULN **OR** creatinine clearance ≥ 30 mL/min (Cockcroft-Gault calculation)
    - Bilirubin level < 1.5 X ULN.
    - AST and ALT < 2.5 X ULN
19. ECOG performance status 0-2
20. Age >16 years

21. Written informed consent prior to admission into the study

4.2.2 Exclusion Criteria

1. Primary or secondary CNS lymphoma
2. T-cell rich B-cell lymphoma
3. Plasma cell leukaemia
4. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
5. Primary amyloidosis
6. Clinically significant (in the opinion of the investigator) cardiovascular disease, such as:
    - History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty/stenting/bypass grafting within the past 6 months prior to the date of consent
    - Class III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system
    - Severe cardiac arrhythmia requiring medication or severe conduction abnormalities
    - Poorly controlled hypertension (resting diastolic blood pressure >100 mmHg)
    - Clinically significant valvular disease, cardiomegaly, ventricular hypertrophy, or cardiomyopathy, QTc prolongation [defined as a QTc interval >450 msec (males) or >470 msec (females)] or other significant ECG abnormalities including 2nd degree (type II) or 3rd degree AV block or bradycardia (ventricular rate <50 beats/min)
7. Clinically significant (in the opinion of the investigator) cerebrovascular disorders or vascular dementia
8. Clinically significant (in the opinion of the investigator) intercurrent medical or psychiatric illness, including serious active infection
9. Significant neuropathy (Grade 3, Grade 4, or Grade 2 with pain)
10. Concurrent treatment with other experimental drugs
11. A daily requirement for prednisone at a dose of >10 mg/day (or steroid equivalent) at time of starting the first dose of study drug. Higher doses are permitted for primary disease symptomatic control during the screening period, after discussion with the medical monitor, but this must have been tapered to a dose of ≤10mg/day by the time treatment with DTP3 starts
12. Stem cell transplant (autologous/allogeneic) or CAR T-cell regimen within 12 weeks of the date of consent
13. Participation in another clinical trial with any investigational drug within 28 days prior to the date of consent
14. Prior (non-experimental) MM or DLBCL therapy within 28 days of the date of first dose of DTP3. Concomitant bisphosphonate therapy is permitted
15. Prior radiotherapy within 28 days of the date of consent. Localised palliative radiation therapy to a single site for symptomatic control is acceptable within this period
16. Anticipated need for concurrent radiotherapy during the study

17. Past or current history of other neoplasms, except for
    - Curatively treated non-melanoma skin cancer
    - Adequately treated *in situ* carcinoma of the cervix
    - Prostate adenocarcinoma with documented PSA value of <0.1 ng/mL within six weeks of the date of consent
    - Other cancer curatively treated, and with no evidence of disease for at least 3 years before the date of consent
18. Known HIV infection
19. Active hepatitis C virus (HCV) or hepatitis B virus (HBV). Patients who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result
20. Ability to become pregnant (or already pregnant or lactating). However, those female patients who have a negative serum or urine pregnancy test before enrolment and agree to use two highly effective forms of contraception: **i**) oral, injected or implanted hormonal contraception [resulting in the inhibition of ovulation] and condom, **ii**) have an intra-uterine device and condom, **iii**) vasectomised partner [provided that the vasectomised partner is the **only** sexual partner of a woman of child bearing potential and that the vasectomised partner has received medical confirmation of surgical success or **iv**) **complete** sexual abstinence [sexual abstinence is considered a highly effective method **only** if defined as refraining from heterosexual intercourse: periodic abstinence (calendar, symptothermal, post-ovulation methods) is **not** acceptable] during the trial and for 6 months after the last dose of DTP3 are considered eligible. Where age appropriate, female patients must be given advice on potential germ cell donation and cryopreservation.
21. Male patients with partners of child-bearing potential [unless they agree to take measures not to father children by using one form of highly effective contraception (condom plus spermicide) during the trial and for 90 days after the last date of DTP3]. Where age appropriate, male patients must be given advice on potential germ cell donation and cryopreservation, Men with pregnant or lactating partners should be advised to use barrier method contraception (for example, condom plus spermicidal gel) to prevent exposure to the foetus or neonate.

4.3 Withdrawal criteria:

4.3.1 Withdrawal of treatment

Study treatment may be withdrawn by the investigator for any reason judged to be in the patient's best interests.

Typical criteria for stopping therapy would include (but not be limited to):

- Unacceptable (drug related) toxicity
- Clinical reasons not related to DTP3
- Evidence of disease progression
- Symptomatic deterioration
- Pregnancy
- Withdrawal of patient consent for further treatment

Withdrawal of treatment is **not** the same as withdrawal from the study and all patients stopping therapy should be encouraged to continue with protocol specified follow-up procedures.

4.3.2 Withdrawal from study

The investigator must make every reasonable effort to keep each patient on study for the whole duration of the trial. However, if the investigator removes a patient from the study or if the patient declines further participation, final off-study assessments should be performed before the start of any alternate non-protocol therapeutic intervention. All the results, evaluations and observations, together with a description of the reasons for withdrawal, must be recorded in the medical records and the electronic case report form (eCRF).

The following are recognised reasons for the investigator to withdraw a patient from the study:

- Withdrawal of patient consent for further study participation
- Serious violation of the study protocol (including persistent patient attendance failure AND/OR persistent non-compliance)
- Sponsor's decision to terminate the study
- Clinical reasons not related to DTP3
- Lost to follow up
- Death

4.4 Patient Replacement

During the dose escalation stage, non-DLT evaluable patients will be replaced.

During the dose expansion stage, non-response evaluable patients may be replaced, after discussion with the medical monitor, (up to a study maximum of 72 patients).

5. TREATMENT

This is a multi-centre Phase I/IIa dose escalation and subsequent cohort expansion study. Up to 37 DLT evaluable patients with MM or DLBCL will be entered into an initial dose escalation stage. A DLT evaluable, patient must have received at least 10 of the 12 scheduled Cycle 1 doses of DTP3 (unless a DLT prevented further DTP3 dosing). Subsequently at least 24 response evaluable patients with MM and at least 24 response evaluable patients with diffuse large B-cell lymphoma will be entered into an open label expansion stage. A response evaluable patient is defined as one who has completed at least one response assessment after at least two cycles of DTP3 or has documented disease progression at an earlier time point.

In both stages, DTP3 will be administered as a one-hour infusion three times per week (with an inter-dose interval of 40 h to 72 h, with a larger interval due to non medical reasons if approved by the medical monitor)**.**

The patient's most recently available weight should be used when calculating the amount of DTP3 to administer (see Pharmacy Manual for details of how to calculate the amount of DTP3 to be used). The weight used to calculate the dose of DTP3 can have been taken up to 10 days prior to administration of the first dose of each cycle.

Treatment for any individual patient will comprise continuous four-week cycles until disease progression (as defined in Appendices A and B), unacceptable (drug related) toxicity, or study termination, whichever occurs first.

Should a patient achieve a CR (DLBCL) or ≥PR (MM) of at least 12 weeks duration, the TDSMC will review all available data for that patient (AEs, clinical efficacy, PK, PD, DTP3 dose intensity) and make a recommendation to the relevant investigator about whether to reduce the frequency of DTP3 administration.

5.1 Dose Escalation Stage

Patients will be administered DTP3 intravenously (i.v.), given as a one hr infusion three times per week (with an inter-dose interval of a minimum of 40 hr and a maximum of 72 hr) in continual 4-week cycles until disease progression or unacceptable toxicity, whichever occurs first.

In the dose escalation stage, the following maximum potential range of DTP3 dose levels will be examined:

2.0, 4.0, 6.0, 9.0, 12.0, 16.0, 20.0, 30.0, 45.0, 67.0, 98.0 mg/kg

The dose escalation will employ a flexible Bayesian Continuous Reassessment Methodology (CRM) to obtain the Maximum Tolerated Dose (MTD) of DTP3 associated with a target Dose Limiting Toxicity (DLT) of 30% from a range of up to 11 doses.

A TDSMC (Section 5.4) will review, on an ongoing basis, all available safety and efficacy/PD/PK data.

For the proposed design, the first patient will be given a starting dose of 2.0 mg/kg. If no DLT occurs, the next patient will only be dosed at the next higher dose after the preceding patient has completed 4 weeks of treatment.

The TDSMC may recommend increasing the number of patients at specific tolerable doses, to obtain further information to aid dose selection or evaluation of doses which are intermediate to the pre-specified dose levels in order to further characterise the relationship between dose level and emergent toxicities.

If a DLT is observed at any dose level, dose escalation will revert to 3 patients per cohort (including the cohort with the initial DLT) to further assess the observed safety data. Once a DLT has been observed, the CRM model will commence estimating the DLT rate at each dose level and recommend the next best dose level with an estimated DLT rate closest to 30% for subsequent patients, using all the accrued DLT data at all doses. An empiric dose-toxicity model $F(\chi,\beta)=\chi^{\exp(\beta)}$, $0<\chi<1$ will be used, where the slope parameter β is assumed to follow a normal distribution with prior mean 0 and a pre-specified prior variance of 1.

The first patient in each cohort will not be enrolled until all patients at the immediately lower cohort have completed the DLT monitoring period and the TDSMC has reviewed the safety data to decide whether to proceed to the next dose level.

The CRM will continually re-estimate the MTD using all accrued DLT data during both the dose escalation and dose expansion stages.

At any time during the dose escalation stage, the TDSMC may recommend initiation of one or both expansion cohorts (MM and/or DLBCL) if it considers that a sufficiently strong efficacy signal and acceptable safety profile has been confirmed at that dose level (which will then be designated the RP2D level).

In this situation the TDSMC will decide whether the dose escalation stage should continue in parallel with the expansion stage, in order to further define the safety and tolerability of DTP3 up to a maximum tolerated dose, if this has not yet been determined.

If the TDSMC does not recommend a RP2D level prior to identification of the MTD, the committee will convene following determination of an MTD to review all available safety, efficacy, PK and PD data and formally recommend an RP2D level to take into the dose expansion stage. The **same** RP2D level will be evaluated in both the MM and DLBCL cohorts.

5.1.1 Dose Limiting Toxicities

Dose Limiting Toxicities (DLTs) are defined as the following events occurring within the first 28 days of dosing of DTP3, *i.e.* up to the end of Cycle 1, corresponding to 12 doses of DTP3 and which are considered to be at least **probably** related to DTP3:

- Any Grade 4 non-haematological adverse event not resolving to at least Grade 3 within 48 hrs
- Any Grade 3 non-haematological event not resolving to at least Grade 2 within 14 days

  Excluding:

  - Grade 3 nausea
  - Grade 3 anorexia
  - Grade 3 or 4 vomiting in patients who have not received optimal treatment with anti-emetics
  - Grade 3 or 4 diarrhoea in patients who have not received optimal treatment with anti-diarrhoeal agents
  - Grade 3 fatigue
  - ≥Grade 3 laboratory abnormalities considered by the Investigator to be **not** clinically relevant
  - ≥3 Grade 3 laboratory TLS if corrected by institutional management
- Grade 4 neutropenia for more than 7 days despite optimal growth factor support
- Grade 4 thrombocytopenia for more than 14 days (with or without platelet support) or associated with active bleeding at any time
- Any other toxicity judged by the TDMSC to be dose limiting in nature
- Death

To be **DLT evaluable**, a patient must have received at least 10 of the 12 scheduled doses of DTP3 (unless a DLT prevented further DTP3 dosing). Non-evaluable patients will be replaced for DLT estimation purposes but may remain in the study.

5.2 Dose Expansion Stage

Following the identification of a suitable dose level of DTP3 for further clinical evaluation, two expansion cohorts will be recruited, consisting of at least 24 response evaluable patients with MM and at least 24 response evaluable patients with diffuse large B-cell lymphoma. A response evaluable patient is defined as one who has completed at least one response assessment after at least two cycles of DTP3 or has documented disease progression at an earlier time point.

Each patient will receive DTP3 until disease progression or unacceptable toxicity, whichever occurs first.

Patients who belong to either cohort and are dosed at the eventual RP2D during the dose escalation stage will contribute to the analysis in the expansion phase (DLBCL patients must meet the eligibility criteria for the expansion stage – *i.e*. have a non-GCB gene signature).

Ongoing safety data will be reviewed by the TDSMC during the dose expansion stage, with a frequency of no less than every seven patients (across both cohorts) who have been treated for at least 8 weeks with DTP3 (*i.e. maximum of* 2 cycles of treatment). Dose delays due to DTP3 related toxicity are included as part of the 8-week period [*i.e* if there is a dose delay during the 8-week period, a patient will still be reviewed for safety even though they may not have received two complete cycles of DTP3].

The safety data will also be reviewed on a continual basis by the medical monitor and should a potential safety signal emerge, an *ad hoc* meeting of the TDSMC will be requested.

5.4 TDSMC and Dose Selection

A Trial Data and Safety Monitoring Committee (TDSMC), consisting of all investigators (or their designee), the Chief Investigator (CI) and Sponsor scientific representatives will be constituted. Further details of the composition and function of the TDSMC are contained in a separate TDSMC charter.

Dose Escalation Stage

The TDSMC will review available safety, PK, PD, and clinical data at the completion of each dose level cohort and make a recommendation to the Sponsor as to whether escalation to the next CRM recommended dose level should occur.

The TDSMC may also recommend increasing the number of patients at specific tolerable dose levels, to obtain further information to aid dose selection or evaluation of doses which are intermediate to the pre-specified dose levels in order to further characterise the relationship between dose level and emergent toxicities.

In the event of sufficiently compelling pharmacodynamic or clinical efficacy (with an acceptable safety profile) at a particular dose level, the TDSMC may recommend that particular dose level for the expansion stage, prior to the determination of a maximum tolerated dose, or completion of the scheduled range of dose levels. In this situation the TDSMC will decide whether the dose escalation stage should continue in parallel with the expansion stage, in order to further define the safety and tolerability of DTP3 up to a maximum tolerated dose (although any such findings will **not** lead to a reappraisal of the already determined RP2D level for the dose expansion stage).

Dose Expansion Stage

Ongoing safety data will be reviewed by the TDSMC during the expansion stage, with a frequency of no less than every seven patients (across both cohorts) who have been treated for at least 8 weeks with DTP3 (*i.e.* 2 cycles of treatment). Dose delays due to DTP3 related toxicity are included as part of the 8-week period [*i.e* if there is a dose delay during the 8-week period, a patient will still be reviewed for safety even though they may not have received two complete cycles of DTP3].

5.5 Patient Withdrawal and Replacement

All patients should be treated until disease progression or unacceptable toxicity, whichever occurs first.

During the dose escalation stage, to be **DLT evaluable**, a patient must have received at least 10 of the 12 scheduled doses of DTP3 during Cycle 1 of treatment (in the absence of a DLT having interrupted DTP3 dosing). Non-evaluable patients will be replaced for DLT estimation purposes but may remain in the study.

During the dose expansion stage, patients who are withdrawn for reasons of disease progression and/or unacceptable toxicity will not be replaced. Patient who are not response evaluable may be replaced, after discussion with the medical monitor.

5.6 Dispensing and Accountability

DTP3 will be packaged, labelled, stored, and distributed by Curia (Todd Campus, West of Scotland Science Park, Glasgow, UK, G20 0XA) to each trial site. DTP3 will be provided to individual site pharmacies in single-use glass vials containing 4 mL of DTP3 at a concentration of 80 mg/mL. The pharmacy will be required to dispense DTP3 into infusion bags of 0.9% saline, based on dose and patient weight (details will be provided in the DTP3 Pharmacy Guidelines Document). The individual site pharmacy will be responsible for accountability and destruction of the drug at their site, as detailed in the DTP3 Pharmacy Guidelines document.

5.7 Dose Modification

Dose Escalation Stage Only

- No dose reductions are permitted for any patient during the DLT evaluation period [Cycle 1 of DTP3).
- Patients experiencing a DLT may remain in the study at the originally assigned dose of DTP3 or a lower dose according to investigator judgement.

Patients initially entered into the study at a DTP3 dose level lower than the one currently being evaluated may increase their DTP3 dose level [provided they have not experienced a DLT during the DLT evaluation period] by one dose level increment per cycle, at the end of each cycle of treatment, at the discretion of the investigator, provided the DTP3 dose remains at least one level below the highest dose currently being evaluated**Dose Escalation and Expansion Stage**

- Up to **three** dose level reductions are permitted in the event of DTP3 related toxicity, at the discretion of the investigator.
- During the **dose escalation stage**, [for patients who have completed the initial DLT evaluation period] each dose reduction should be to the immediately preceding dose level specified in the DTP3 dose level escalation range [*e.g.* 20mg/kg reduced to 16mg/kg; 16mg/kg reduced to 12mg/kg *etc*]
- For the **dose expansion stage**, the TDSMC will specify a dose reduction algorithm at the time the RP2D level is determined, taking account of the actual RP2D level and the pattern of toxicities seen at lower dose levels during the dose escalation stage.
- Dose reductions are permitted for the following toxicities if they are considered clinically relevant by the investigator:
    - Any Grade 4 adverse event not resolving to at least Grade 3 within 48 hr
    - Any Grade 3 adverse event not resolving to at least Grade 2 within 14 days
    - Any dose delay greater than 7 days
- Any potential dose reduction must be discussed in advance with the Medical Monitor and (if judged appropriate by the investigator and medical monitor) the Chief Investigator too.
- If a dose level is reduced, it may be increased again (to the immediately preceding dose level), at the discretion of the investigator, if there is complete resolution of the original toxicity leading to the dose reduction.

- Dose delays of up to 14 days are permitted for the resolution of DTP3 related toxicity. Patients requiring a dose delay greater than 14 days should be withdrawn from the study. Dose delays of greater than 14 days for reasons other than toxicity (*e.g.* logistical ones) must be discussed with and approved by the medical monitor.

5.8 Interaction with Other Drugs

The potential of DTP3 to interact with concomitant medication has been studied *in vitro*. DTP3 does not inhibit the cytochrome P450 isoforms, CYP1A2, 2B6, 2C8, 2C9, and 3A4, in human liver microsomes, when tested up to the maximum concentration of 25 µM. Only a minor time dependant inhibition of CYP3A4 was observed. DTP3 did not induce the cytochrome P450 isoforms, CYP3A4, 2B6 and 1A, in human hepatocytes to a significant degree, when tested at concentrations up to 10 µM.[43]

DTP3 was evaluated for its potential to act as a substrate or inhibitor of a range of cell transporters. DTP3 was neither a substrate nor an inhibitor of the majority of transporters evaluated. DTP3 was a substrate for SLC uptake transporters, OAT1B3, MATE-1 and MATE2-K, at 10 µM, but not at lower concentrations. Some inhibitory potential of DTP3 was noted for MATE1 and MATE2-K, with IC_{50} values of 11 µM and >100 µM, respectively.

Overall, the potential for DTP3-associated drug interaction is considered to be low based on the high IC50 values observed.

5.9 Recommended prophylactic medication/pre-medication

No specific premedication is recommended prior to administration of DTP3, although institution specific policies pertaining to premedication prior to intravenous administration are permitted.

Institution specific prophylaxis policies (*e.g.* antibiotics, anti-virals, PCP-prophylaxis *etc*) are permitted.

5.10 COVID19 Vaccination/Testing

Institutional policies for routine COVID19 testing should be followed.

There are **no** protocol limitations to the timing of COVID19 vaccination, relative to initial or subsequent dosing with DTP3, which should be implemented according to the clinical judgement of the investigator.

6. PHARMACOVIGILANCE

6.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. *All AEs judged by either the reporting Investigator or the medical monitor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*

Abnormal laboratory values should only be recorded as AEs if they are judged to be clinically significant by the investigator or delegated sub-investigator. An abnormal value would normally be considered clinically significant if it necessitates any change to the participant's treatment, if it is symptomatic, if it is deemed related to a protocol specified intervention or otherwise at the discretion of the investigator.

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (*e.g.* investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product*). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.*

Serious Adverse Event (SAE) or **Serious Adverse Reaction (SAR):** any untoward medical occurrence or effect that at any dose:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

6.2 Causality

The assignment of causality should be made by the Investigator responsible for the care of the participant using the definitions in the table below.

In the case of discrepant views on causality between the Investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

6.3 Reporting Procedures

All adverse events should be reported during the period from the date of consent to 28 days after the last dose of DTP3. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the trial manager in the first instance. A flowchart is given (Safety Reporting Overview) to aid in the reporting procedures. An EDC System will be used for adverse event reporting. Sites will be expected to complete the AE eCRFs using the relevant database and indicating whether it is an SAE or not. SAEs require additional paper reporting. The completed SAE forms should be emailed to the safety reporting inbox (contact details on Safety Reporting Overview), the Trial Manager and CI immediately.

All AEs should be followed up until they have resolved (or stabilised, as some AEs may be ongoing at end of study).

6.3.1 Non serious AR/AEs

All such toxicities, whether expected or not, should be recorded in the Adverse Event eCRF which is completed by site staff and signed by the site PI.

6.3.2 Serious AR/AEs

For the purposes of this clinical study, all SARs will be considered SUSARs.

All SAEs must be reported to the Sponsor immediately (within 24 hours of the site becoming aware of the event). At a minimum, the following information should be included: nature of event, date of onset, severity, corrective therapies given, outcome and causality (*i.e.* unrelated, unlikely, possible, probably and definitely). The responsible investigator should sign the causality of the event. Additional information should be sent to the Sponsor within 5 days, if the reaction has not resolved by the time of reporting.

6.3.3 SAEs

It is the investigator's responsibility to report all SAEs to the Trial Manager and CI immediately (within 24 hours of the site team becoming aware of it). It is the Trial Managers responsibility to then report this to the Sponsor immediately.

If an adverse event is classed as serious, the AE form in the eCRF is completed and the SAE box ticked. At the point an AE is classed as serious, an email automatically goes to the Project Team to inform them of this. Additionally, a detailed SAE paper form then required completing by the site staff and site PI. This form is reviewed by the PI, who adds their comments and diagnosis before signing it off. This paper form must be emailed to the Trial Manager and CI within 24 hours of the site team being made aware of the SAE, who subsequently inform the Sponsor.

Additional information should be sent to the Trial Manager and CI, and additionally forwarded onto the Sponsor within 5 days, if the reaction has not resolved by the time of initial reporting.

Disease progression and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

6.3.4 SUSARs

It is the investigator's responsibility to report all SUSARs to the Trial Manager and the CI or CI delegate:

- The site staff and site PI must complete the SAE form (in addition to the AE eCRF with SAE box ticked), and send it immediately (within 24 hours and via email) signed and dated, together with the relevant treatment forms and anonymised copies of all relevant investigations.

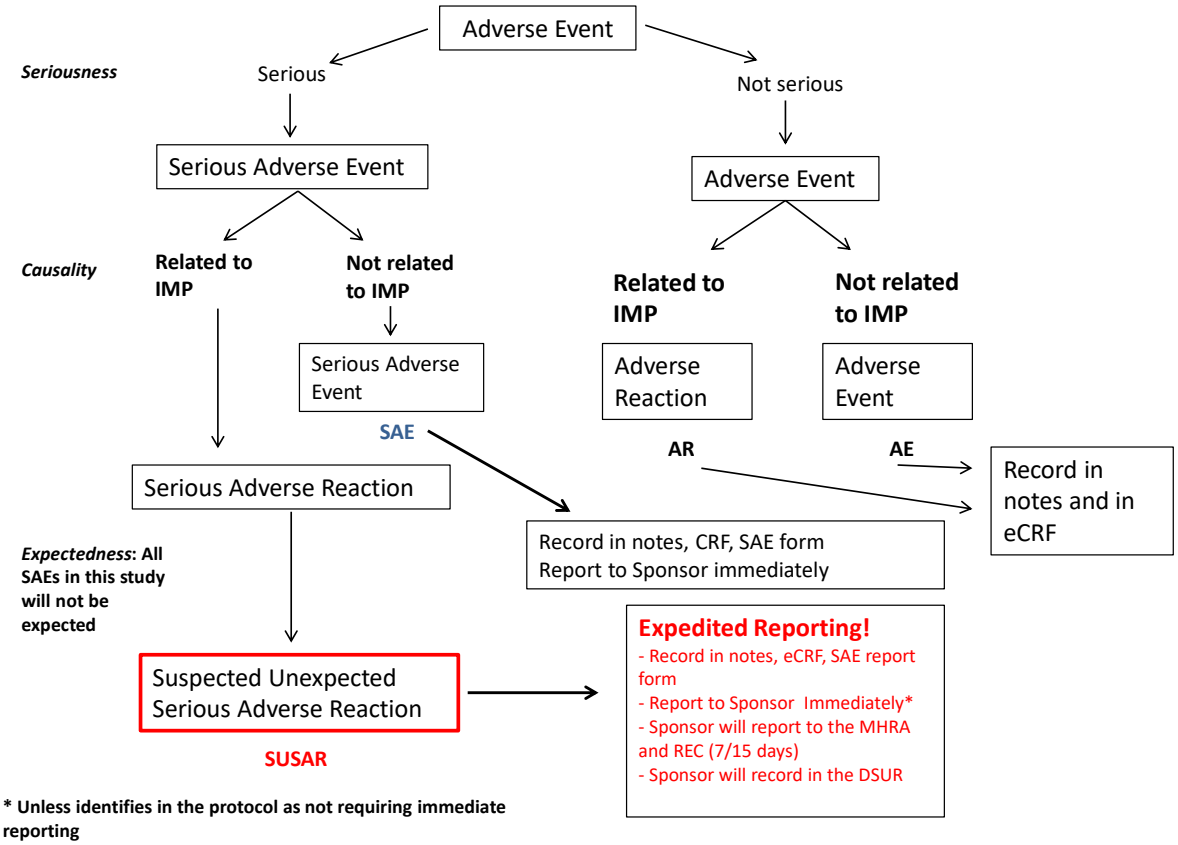
OR

- Contact the Trial Manager by phone and then send the completed SAE eCRF within 24 hours as above

It is the Trial Managers responsibility to:

- Inform the Sponsor of all SUSARs
- Ensure that the CI/CI delegate has reviewed and signed off all SUSARs prior to reporting to MHRA and REC
- Notify the MHRA and REC of all SUSARs occurring during the study, according to the following timelines; fatal and life-threatening, within 7 days of notification, and non-life threatening, within 15 days.
- Inform all investigators of all SUSARs occurring throughout the study.

Safety Reporting Overview



Contact details for reporting SAEs and SUSARs:

Email: RGIT.ctimp.team@imperial.ac.uk & dtp3-safety@imperial.ac.uk

In addition, please contact:

Clinical Project Manager

e.hadley@imperial.ac.uk

Tel: 07873627283

Chief Investigator (Dr Aris Chaidos):

a.chaidos@imperial.ac.uk

7. ASSESSMENT AND FOLLOW-UP

Study Assessments and relevant timings are detailed below. In the event that protocol specified procedures and/or timings cannot be adhered to, due to any prevailing COVID19 restrictions, these will **not** be considered protocol deviations but will be documented in a specific COVID19 section of the eCRF.

7.1 Safety Assessments (Dose Escalation Stage)

7.1.1 Laboratory safety analysis

Haematology (FBC), biochemistry and urinalysis will be performed WEEKLY in Cycle 1 of treatment EVERY OTHER WEEK during Cycle 2 and then 4-WEEKLY thereafter from Cycle 3 onwards. Testing can be performed within a 72 hour time frame before the next scheduled Day 1 of dosing),

For myeloma patients the following tests must be performed no more than 72 hours prior to day 1 of dosing:

- Serum Protein Electrophoresis (SPEP)
- Paraprotein Quantification
- Serum Immunofixation
- Serum Immunoglobulin Levels
- Serum Free light chains
- 24h urine Bence Jones protein

Coagulation (aPTT, PT) will be assessed 4-WEEKLY.

Serum pregnancy test (where appropriate) at beginning of each cycle of DTP3 and then monthly for six months after cessation of DTP3 therapy.

7.1.2 Blood Pressure and Pulse Rate and 12 Lead ECG

These will be performed according to the following schedule (+/- 5 minutes):

Cycle 1: Week 1 and Week 2	Day 1, Day 3, and Day 5 (15 min before and 30 min, 60 min, and 120 min after the end of each DTP3 infusion)
Cycle 1: Week 3 and Week 4	15 min before and 30 min after the end of each DTP3 infusion
Cycle 2 onwards	15 min before and 30 min after the end of each DTP3 infusion

7.1.3 Adverse Events and Concomitant Medications

Prior to each DTP3 infusion (with follow up of ongoing AEs as necessary after completion of DTP3 therapy).

7.2 Safety Assessments (Expansion Stage)

7.2.1 Laboratory safety analysis

Haematology, biochemistry and urinalysis will be performed WEEKLY in Cycle 1 of treatment (within a 72 hour time frame, up to 3 days prior to infusion), EVERY OTHER WEEK during Cycle 2, and then 4-WEEKLY thereafter from Cycle 3 onwards. Testing can be performed within a 72-hour time frame before the next scheduled Day 1 of dosing),

Coagulation (aPTT, PT) will be assessed 4-WEEKLY.

Serum pregnancy test (where appropriate) at beginning of each cycle of DTP3 and then monthly for six months after cessation of DTP3 therapy.

7.2.2 Blood Pressure and Pulse Rate and 12 Lead ECG

These will be performed 15 min (+/- 5 min) before and 30 min (+/- 5 min) after the end of each DTP3 infusion for Doses 1, 2 and 3 (Week 1) and then before the first dose of DTP3 at the beginning of Week 2 onwards [*i.e* before Dose 4, Dose 7, Dose 10 *etc*]

7.2.3 Adverse Events and Concomitant Medications:

Prior to each DTP3 infusion (with follow up of ongoing AEs as necessary after completion of DTP3 therapy).

7.3 Pharmacokinetics

Blood samples (4 mL) will be taken for the analysis of DTP3 levels during Cycle 1 of DTP3 dosing. Where possible, patients will be admitted overnight on Day 1 of Cycle 1 to permit prolonged blood sampling for PK analysis.

Blood samples will be collected according to the following schedule:

Cycle 1 Day 1:

Pre-infusion, 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, 16 hr and 24 hr post- infusion

It is anticipated that full overnight PK sampling will be performed in nearly all patients, although this is at the discretion of each investigator. For exceptional patients who cannot be hospitalised (for logistical reasons), the following outpatient schedule will be adopted:

Pre-infusion, at 5 min, 15 min, 30 min, 1 hr, 2 hr and 4 hr post- infusion

Cycle 1 Day 3:

Pre-infusion

Cycle1 Day 5:

Pre-infusion, and at 0.5 hr, 1 hr, 2hr and 4 hr post- infusion

Blood samples will be collected by direct venepuncture or from an indwelling cannula into a labelled tube containing the appropriate anticoagulant, Further details will be provided in the separate DTP3 pharmacokinetic blood sampling manual.

For PK samples taken during the first hour of sampling, these samples need to be taken as precisely as possible at the specified time points, ideally within a window of +/- 2 minutes. For samples taken after the first hour and up to 8 hours, there can be a small window of +/- 5 minutes, for samples taken at 12 hours and later a window of 30 minutes is allowed. The exact time of bleeding will anyway be always registered on the log for all patients.

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The blood samples will be processed, split, stored and shipped according to the sample processing instruction document mentioned above.

7.4 Pharmacodynamics

Mandatory samples (unless technically not possible) for pharmacodynamic (PD) assessment will be taken as follows:

- At **screening** (within 28 days prior to DTP3 treatment)
- **24 hours** (range 18-36 hr) after the **fourth dose** of DTP3 treatment (Cycle 1, Week 2, Day 2)

Tissue will be collected as follows on each occasion for PD, genetic and biomarker assessment and sent in their entirety to the Hammersmith site (Prof Guido Franzoso's lab):

- MM: 50 mL of blood and 10 mL of bone marrow aspirate
- DLBCL: 50mL of blood and a tumour biopsy (18G core), if accessible.

7.5 Efficacy Assessments

7.5.1 MM

Routine efficacy assessments will be performed every 4 WEEKS (see Trial Assessment Schedule, Appendix C) unless clinically indicated at an earlier time point. The following assessments will be performed on a 4-weekly basis:

- Serum protein electrophoresis and paraprotein quantification
- Serum free light chain
- 24h urine collection electrophoresis (only in patients with detectable urinary M protein at screening)
- Biochemistry panel
- Full Blood Count

The necessity for bone marrow aspirate and biopsy and/or radiological imaging will be determined by the patient's individual clinical course and will only be undertaken when judged appropriate by the investigator for determination of response or progression, as follows:

If a complete (or stringent complete) response is suspected:

Two independent measurements (according to normal institutional practice) are required to confirm:

- negative immunofixation: serum
- negative immunofixation: urine

If these two independent measurements are consistent with the definition of a complete response, then a bone marrow aspirate and biopsy should be performed

If progression is suspected:

This can be determined by measurement of any relevant disease parameter, including radiological imaging and/or bone marrow plasma cell percentage, but should be confirmed by two independent measurements, according to normal institutional practice.

7.5.2 DLBCL

FDG-PET/CT imaging will be performed every 8 WEEKS after the first dose of DTP3, unless clinically indicated at an earlier time point (*e.g.* if there is clinical suspicion of disease progression).

A bone marrow aspirate and biopsy is required for confirmation of radiological complete response in patients who had a positive bone marrow aspirate/biopsy at screening.

Response assessment at each FDG-PET/CT timepoint will be made according to the Lugano 2014 criteria (Appendix B).

7.6 End of Treatment Visit

Following cessation of DTP3 therapy, for any reason other than death, all patients will have an End of Treatment Visit performed within a minimum of 3 days and a maximum of 28 days of the last dose of DTP3. The End of Study Visit must take place BEFORE the next treatment regime starts.

If the EOS visit takes place before day 28 post-DTP3 treatment, an EOS safety call will additionally take place. This safety call should occur on or just after day 28 after completing DTP3 treatment, to capture any final AEs covering the period of 28 days following the final DTP3 dose. Alternatively, this call can take place immediately before the patient is to commence a new treatment regime should a new treatment be planned to begin within 28 days of completing DTP3.

The following assessments should be performed:

- 12-Lead ECG
- Vital Signs (Blood Pressure, Pulse Rate)
- Symptom directed physical examination, including ECOG performance status
- Adverse Events and Concomitant Medications
- Pregnancy Test (where appropriate)
- Discussion with the patient of any clinically relevant incidental findings detected during the course of the study (if not already discussed with the patient at an earlier timepoint).

Should a participant be starting a new treatment drug after DTP3 treatment, there is a strict minimum washout safety period after the final dose of DTP3 of 5 days. This wash-out period has been selected based on at least 5-times the elimination half-life (t1/2) of DTP3. A final safety follow-up period of 5 days after the last dose of DTP3 is therefore required if the patient needs to start a new treatment before the scheduled 28-day safety follow-up. Starting a new treatment within this 5-day washout period would be classified as a serious protocol violation and subject the patient to potential drug interactions, this must be avoided. Therefore, any new drug treatments should start after the minimum 5 days washout period from DTP3, with the final AE check conducted immediately prior to commencing the new treatment if this is within 28-days of completing DTP3.

7.7 Follow Up

All patients who do not have disease progression at the time of ceasing DTP3 treatment will be followed, through routinely scheduled clinic visits for disease progression [according to the schedule in 7.5 above] and survival for a period of six months after the last patient has been recruited into the study.

Patients with disease progression at the time of ceasing DTP3 treatment will be followed up through routinely scheduled clinic visits for subsequent anti-cancer therapies and survival.

Patients' disease progression and survival status should be followed up a minimum of every 6 months, but ideally every 3-4 months through their attendance at routine clinic appointments.

Patients not being actively followed in the clinic will be contacted (or *via* a family member as appropriate) at approximately 2-3 monthly intervals to assess survival status.

Every effort should be made to follow-up patients who have entered the trial. It is the responsibility of the investigator at site to ensure that the follow-up data required by the protocol are collected and reported.

After the study has completed and final results are available, investigators may share these at the request of individual patients.

7.8 Trial Closure

The trial will be declared closed when either **i**) the last surviving patient either dies or **ii**) is withdrawn from the trial, or **iii**) six months after the last patient has been recruited into the study or **iv**) the Sponsor decides to terminate the study, whichever occurs first.

7.9 Carry-over Protocol

If, at the time of trial closure, there are sufficient patients still deriving clinical benefit (in the opinion of the relevant investigators) from DTP3 therapy, the Sponsor may roll them over into an extension protocol, although the decision to do this will be at the sole discretion of the Sponsor.

8. STATISTICS AND DATA ANALYSIS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written and approved describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described in this section and should be considered the definitive point of reference for all statistical analyses.

Appropriate descriptive methods will be used to summarise the data obtained in this study. Continuous variables will be presented by descriptive statistics including the number of observations, arithmetic mean, standard deviation, minimum, median and maximum. Categorical variables will be summarised by frequency and percentage.

8.1 Justification for sample size

Dose Escalation

The performance of the proposed two-stage CRM was assessed by simulations. Initial simulations gave a good performance for determining the correct MTD at least 55% of the time for up to 24 patients under seven clinically relevant scenarios (more details can be found in the Statistical Simulation Plan). Most patients are dosed at the recommended MTD. If all doses are too toxic, the design will correctly stop 60% of the time.

Dose Expansion

It is estimated that 24 patients per indication [MM and DLBCL] in the expansion phase produces a one-sided 90% lower-limit confidence interval of at least 27.7% when the observed response rate is ≥41.7% using the Exact Clopper-Pearson interval method. This exceeds the minimum response rate of 25% required to justify further testing for each cohort.

8.2 Analysis Sets

Three study populations will be defined:

- Three study analysis sets will be defined:
- **The safety analysis set** will be used as the analysis population for all safety endpoints and comprises all patients who receive at least one dose of DTP3.
- **The efficacy analysis set** will include all patients who receive at least one dose of DTP3 and will be used as the analysis population for efficacy endpoints.
- **The per protocol analysis set** will be used as a sensitivity analysis for efficacy and pharmacodynamic endpoints and comprises patients who:

- The **per protocol analysis set** will be used as a sensitivity analysis for efficacy and pharmacodynamic endpoints and comprises patients who:
    - Fulfil all the inclusion and none of the exclusion criteria
    - Received at least 2 cycles of DTP3 (*i.e*. ≥8 weeks of therapy) or have documented progression at an earlier time point.
- Have at least one efficacy assessment undertaken after ≥8 weeks of therapy or have documented progression at an earlier time point.
- Have completed PD blood and bone marrow (MM) /tumour (DLBCL) sampling (after seventh dose of DTP3)

8.3 Study endpoints

Safety Endpoints

- The MTD will be defined as the dose with an estimated DLT rate closest to the 30% target DLT rate.
- The estimated DLT rate of the MTD and RP2D with 90% probability intervals will be reported.
- Toxicity data (AE, SAE, DLT) will be summarised descriptively by dose level and disease cohort
- Laboratory data will be summarized by CTCAE severity shift (baseline *versus* worst post-baseline grade).
- All adverse event terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and graded using CTCAE version 5.0. All AE data will be listed by dose level, cohort, patient number and onset date. Any AEs occurring on or after first dose of DTP3 will be considered as treatment-emergent adverse events (TEAEs). TEAEs will be summarised by MedDRA system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA Version 18.0). In addition, all serious adverse events, including deaths, will be listed separately and summarised. DLTs will be identified and summarised descriptively.

Efficacy Endpoints

- Efficacy data will be summarised descriptively by dose level and disease cohort
- Patients who are dosed at the RP2D level in the dose escalation stage will contribute to the expansion stage (DLBCL patients must meet the dose escalation eligibility criteria).
- Clinical response will primarily be evaluated using **overall response rate** (ORR), separately for the MM and DLBCL cohorts, defined by the International Myeloma Working Group 2016 (MM) or Lugano 2014 (DLBCL) criteria respectively.
- Exploratory analyses of response in multiple myeloma patients according to their cytogenetics abnormalities and disease risk.
- Point estimates for overall response rates, along with the approximate lower 1-sided 90% confidence intervals will be calculated.
- Time-to-event outcomes for efficacy [time to response, duration of response, progression free survival, event free survival and overall survival] will be analysed using the Kaplan-Meier method.

Pharmacokinetic Endpoints

- Data will be presented descriptively by dose level

DTP3 Exposure

- Relative DTP3 Dose Intensity (delivered dose *versus* intended dose) will be calculated for each patient and presented descriptively by dose level and disease cohort

Pharmacodynamic Endpoints

- Data will be presented descriptively by dose level and disease cohort

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

9. TRANSLATIONAL RESEARCH

Bone marrow aspirates, 50 mL blood samples and tumour biopsies (where appropriate) will be linked pseudonymised and then transferred to Prof. G. Franzoso' s laboratory at Imperial College London and/or other participating sites.

Laboratory processing of blood, bone marrow and tumour biopsy samples are detailed in a separate **Sample Processing Manual.**

10. MONITORING

10.1 Risk assessment

The trial study team has performed a clinical risk assessment to identify the main risks associated with the trial, the study team, IMP dosing, pharmacy, general safety, adverse reactions, invasive procedures and participants. This risk assessment has guided the development of a mitigation plan for each risk identified, as well as the development of a trial monitoring plan.

10.2 Monitoring by the Trial Data and Safety Monitoring Committee (TDSMC)

A TDSMC will be constituted, consisting of all investigators (or their designated representative) and Sponsor scientific representatives.

During the Dose Escalation Stage, the TDSMC will review all patient safety, PK, PD and clinical data at each dose level, after a minimum of one cycle of treatment, and endorse CRM recommendations for escalation to the next scheduled dose level. The TDSMC may also recommend increasing the number of patients at specific tolerable dose levels, to obtain further information to aid dose selection or evaluation of doses which are intermediate to the pre-specified dose levels in order to further characterise the relationship between dose level and emergent toxicities.

In the event of sufficiently compelling PD AND/OR clinical efficacy data at a particular dose level, the TDSMC may recommend that particular dose level for the expansion stage prior to the determination of an MTD, or completion of the scheduled range of dose levels. In this situation, the TDSMC will decide whether the dose escalation stage should continue in parallel with the expansion stage, in order to define the safety and tolerability of DTP3 up to an MTD.

If the TDSMC does not recommend an RP2D level prior to identification of the MTD, the committee will convene following determination of an MTD to review all available safety, efficacy, PK and PD data and formally recommend an RP2D level to take into the dose expansion stage. The same RP2D level will be evaluated in both the MM and DLBCL cohorts.

During the dose expansion stage, the TDSMC will review ongoing safety data with a frequency no less than every seven patients (across both cohorts) who have completed at least two cycles of treatment.

10.3 External Monitoring

Clinical site monitoring will be performed according to the Trial Monitoring Plan. Trial Monitors will be appointed by the Sponsor and are from Imperial College Healthcare NHS Trust. Their role will be to verify adherence to the protocol and the completeness and accuracy of a selection of the data being entered into the electronic Case Report Forms (eCRFs). Any data recorded directly on the eCRFs (where there is no prior written or electronic record of this data), should also be recorded in the medical notes as source data. Trial Monitors will require access to all patients' medical records including laboratory test results. Trial Monitors will also require access to pharmacy records relating to administration of DTP3. The investigator should work with the Trial Monitor to ensure that any problems that are detected are resolved.

11. REGULATORY ISSUES

11.1 CTA

The study will obtain authorisation from the MHRA before commencement of the trial.

11.2 Ethics approval

The Study Coordination Centre will obtain research ethics approval before the trial commences. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Study Coordination Centre will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

11.3 Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent should be obtained in each case. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial, the Principal Investigator remains free to give alternative treatments to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants will remain in the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol without giving any reasons and without prejudicing their further treatment.

11.4 Confidentiality

Participants' identification data will be required for the registration process. The Study Coordination Centre will preserve the confidentiality of all participants taking part in the study and is registered under the Data Protection Act.

11.5 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

11.6 Sponsor

Imperial College London will act as the Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

11.7 Funding

The trial is being funded by the Medical Research Council, through the Biomedical Catalyst: Developmental Pathway Funding Scheme. Patients will be reimbursed for any travel costs associated with the trial.

11.8 Audits and Inspections

The study may be subject to inspection and audit by Imperial College London under their remit as Sponsor. The Study Coordination Centre and other regulatory bodies will ensure adherence to GCP.

12. PUBLICATION POLICY

Following completion of the Study, the Sponsor will ensure the appropriate publication or other dissemination of the conclusions of the Study. Should the Study form part of a study being undertaken at a number of separate sites, this obligation shall arise following completion of the entire Multi-Site Study.

Investigators **shall not** publish or otherwise disseminate the conclusions of the Study, including all or any part of the Results of the Study without the prior written consent of the Sponsor, such consent not to be unreasonably withheld or delayed. Any publication or other dissemination of the conclusions of the Study by investigators **shall not** occur until the Sponsor has published the conclusions of the Study and shall refer to publication by the Sponsor in such form as the Sponsor may reasonably direct. Any publication requests by PI's shall be sent to the Sponsor Scientific Representative in the first instance.

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APPENDIX A: International Uniform Response Criteria for Multiple Myeloma

Stringent complete response

Complete response as defined below **plus** normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††

Complete response

Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates

Very good partial response

Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h

Partial response

≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.

If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required.

Minimal response

≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.

Stable disease

Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease

Progressive disease Any one or more of the following criteria:

- Increase of 25% from lowest confirmed response value in one or more of the following criteria:
- Serum M-protein (absolute increase must be ≥0·5 g/dL);
- Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL;
- Urine M-protein (absolute increase must be ≥200 mg/24 h);
- In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL);
- In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%);
- Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease.

Clinical relapse

Clinical relapse requires one or more of the following criteria:

- Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice
- Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression)
- Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defi ned as a 50% (and ≥1 cm) increase as measured serially by the SPD of the measurable lesion
- Hypercalcaemia (>11 mg/dL)
- Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions;
- Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma;
- Hyperviscosity related to serum paraprotein

Relapse from complete response (to be used only if the end point is disease-free survival)

- Any one or more of the following criteria:
- Reappearance of serum or urine M-protein by immunofixation or electrophoresis;
- Development of ≥5% plasma cells in the bone marrow;
- Appearance of any other sign of progression (*i.e*, new plasmacytoma, lytic bone lesion, or hypercalcaemia see above)

Relapse from MRD negative (to be used only if the end point is disease-free survival)
Any one or more of the following criteria:

- Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma);
- Reappearance of serum or urine M-protein by immunofixation or electrophoresis;
- Development of ≥5% clonal plasma cells in the bone marrow;
- Appearance of any other sign of progression (*i.e.,* new plasmacytoma, lytic bone lesion, or hypercalcaemia)

*Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a 90% decrease in the difference between involved and uninvolved FLC levels.

APPENDIX B: International Working Group Response Criteria for DLBCL (Lugano criteria)

Response and Site	PET-CT-based response	CT-based response
Complete	Complete Metabolic Response	Complete radiological response
Lymph nodes and extra-lymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	All of the following Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extra-lymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology, if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission
Lymph nodes and extra-lymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	All of the following: ≤50% decrease in SPD of up to 6 target measurable nodes and extra-nodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extra-nodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extra-nodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None

Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	All of the following: PPD progression: An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
Extra-nodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	
Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extra-nodal site >1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*****A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extra-nodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extra-nodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2 uptake ≤mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

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APPENDIX C: Trial Assessment Schedule for Patients in the Dose Escalation and Cohort Expansion Stages

		ESCALATION STAGE														
		CYCLE 1														
	Within 28 days prior to first dose	Week 1 Day 1	Week 1 Day 2	Week 1 Day 3	Week 1 Day 5	Week 2 Day 1	Week 2 Day 2	Week 2 Day 3	Week 2 Day 5	Week 3 Day 1	Week 3 Day 2	Week 3 Day 3	Week 3 Day 5	Week 4 Day 1	Week 4 Day 3	Week 4 Day 5
		Dose 1	N/A	Dose 2	Dose 3	Dose 4	N/A	Dose 5	Dose 6	Dose 7	N/A	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12
Initial tests																
Written informed consent	x															
Medical history	x															
Disease specific history (MM/DLBCL)	x															
ECOG Performance Status	x															
Adverse Events		x		x	x	x		x	x	x		x	x	x	x	x
Concomitant medications	x	x		x	x	x		x	x	x		x	x	x	x	x
Physical examination (as per local clinical standards and as considered adequate by the PI)	x															
Height	x															
Weight	x[m]	x[m]				x[m]				x[m]				x[m]		
Blood pressure	x	x[e]		x[e]	x[e]	x[e]		x[e]	x[e]	x[e]		x[e]	x[e]	x[e]	x[e]	x[e]
Pulse rate	x	x[e]		x[e]	x[e]	x[e]		x[e]	x[e]	x[e]		x[e]	x[e]	x[e]	x[e]	x[e]
Respiratory Rate	x															
12-lead ECG	x	x[e]		x[e]	x[e]	x[e]		x[e]	x[e]	x[e]		x[e]	x[e]	x[e]	x[e]	x[e]
Urinalsyis	x	x				x				x				x		
Calculated creatinine clearance	x															
Pregnancy serum (where appropriate) [i]	x															
PT and APTT (coagulation testing)	x															
Full Blood Count (Haematology)																
Haemoglobin	x	x				x				x				x		
Hematocrit	x	x				x				x				x		
WBC count with complete manual or automated differential	x	x				x				x				x		
RBC count	x	x				x				x				x		
Platelet count	x	x				x				x				x		
Biochemistry assessment																
Renal Profile (Sodium, Potassium, Creatinine, Urea, eGFR, blood urea nitrogen)	x	x				x				x				x		
Calcium (bone profile)	x	x				x				x				x		
Uric acid	x	x				x				x				x		
Lactate dehydrogenase	x	x				x				x				x		
Chloride	x	x				x				x				x		
Bicarbonate	x	x				x				x				x		
Glucose	x	x				x				x				x		
LFT (ALT, ALP, Total Bilirubin, Albumin, Total protein, Globulin, AST)	x	x				x				x				x		
Phosphorous	x	x				x				x				x		
DTP3																
IMP administration		x		x	x	x		x	x	x		x	x	x	x	x
PK																
4ml blood sample		x[e]	x[e]	x[e]	x[h]											
MULTIPLE MYELOMA PATIENTS:																
MM-specific assessments [f]																
Serum protein electrophoresis (SPEP)	x	x														
Paraprotein quantification	x	x														
Serum immunofixation	x	x														
Serum immunoglobulin levels	x	x														
Serum free light chains (sFLC)	x	x														
24-hour urine sample for urine proteins and urine immunofixation [g]	x	x														
FDG-PET/CT, whole body MRI, or whole body low-dose CT (unless performed within 8 weeks of treatment starting)	x															
Bone marrow aspirate and biopsy for local determination of plasma cell count	x															
Beta-2 microglobulin level	x															
MM - PD, lab and genetic assessments																
Bone marrow 10mL aspirate	x						x[c]									
50ml blood sample	x						x[c]									
DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS:																
DLBCL specific assessments [f]																
FDG-PET/CT (unless performed within 4 weeks of treatment starting)[j]	x															
Bone marrow aspirate and biopsy [for histological evaluation of DLBCL involvement]	x															
DLBCL - PD, lab and genetic assessments																
Tumour sample (where accessbile)	x						x[c]									
50ml blood sample	x						x[c]									

	ESCALATION STAGE											
	CYCLE 2											
	Week 1 Day 1	Week 1 Day 3	Week 1 Day 5	Week 2 Day 1	Week 2 Day 3	Week 2 Day 5	Week 3 Day 1	Week 3 Day 3	Week 3 Day 5	Week 4 Day 1	Week 4 Day 3	Week 4 Day 5
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12
Initial tests												
Written informed consent												
Medical history												
Disease specific history (MM/DLBCL)												
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination (as per local clinical standards and as considered adequate by the PI)												
Height												
Weight	x[m]			x[m]			x[m]			x[m]		
Blood pressure	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]
Pulse rate	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]
Respiratory Rate												
12-lead ECG	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]
Urinalsyis	x						x					
Calculated creatinine clearance												
Pregnancy serum (where appropriate) [i]	x											
PT and APTT (coagulation testing)	x											
Full Blood Count (Haematology)												
Haemoglobin	x						x					
Hematocrit	x						x					
WBC count with complete manual or automated differential	x						x					
RBC count	x						x					
Platelet count	x						x					
Biochemistry assessment												
Renal Profile (Sodium, Potassium, Creatinine, Urea, eGFR, blood urea nitrogen)	x						x					
Calcium (bone profile)	x						x					
Uric acid	x						x					
Lactate dehydrogenase	x						x					
Chloride	x						x					
Bicarbonate	x						x					
Glucose	x						x					
LFT (ALT, ALP, Total Bilirubin, Albumin, Total protein, Globulin, AST)	x						x					
Phosphorous	x						x					
DTP3												
IMP administration	x	x	x	x	x	x	x	x	x	x	x	x
PK												
4ml blood sample												
MULTIPLE MYELOMA PATIENTS:												
Myeloma-specific assessments [i]												
Serum protein electrophoresis (SPEP)	x											
Paraprotein quantification	x											
Serum immunofixation												
Serum immunoglobulin levels												
Serum free light chains (sFLC)	x											
24-hour urine sample for urine proteins and urine immunofixation [f]	x											
FDG-PET/CT whole body MRI, or whole body low-dose CT (unless performed within 8 weeks of treatment starting)												
Bone marrow aspirate and biopsy for local determination of plasma cell count												
Beta-2 microglobulin level												
PD, lab and genetic assessments												
Bone marrow 10mL aspirate												
50ml blood sample												
DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS:												
DLBCL specific assessments [i]												
FDG-PET/CT [j]												
Bone marrow aspirate and biopsy [for histological evaluation of DLBCL involvement] [h]												
PD, lab and genetic assessments												
Tumour sample (where accessbile)												
50ml blood sample[e]												

	ESCALATION STAGE											
	CYCLE 3 & ONWARDS											
	Week 1 Day 1 Dose 1	Week 1 Day 3 Dose 2	Week 1 Day 5 Dose 3	Week 2 Day 1 Dose 4	Week 2 Day 3 Dose 5	Week 2 Day 5 Dose 6	Week 3 Day 1 Dose 7	Week 3 Day 3 Dose 8	Week 3 Day 5 Dose 9	Week 4 Day 1 Dose	Week 4 Day 3 Dose 11	Week 4 Day 5 Dose
Initial tests												
Written informed consent												
Medical history												
Disease specific history (MM/DLBCL)												
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (as per local clinical standards and as considered adequate by the PI)												
Height												
Weight	X[a]			X[a]			X[a]			X[a]		
Blood pressure	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Pulse rate	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Respiratory Rate												
12-lead ECG	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Urinalysis	X											
Calculated creatinine clearance												
Pregnancy serum (where appropriate)[i]	X											
PT and APTT (coagulation testing)	X											
Full Blood Count (Haematology)												
Haemoglobin	X											
Hematocrit	X											
WBC count with complete manual or automated differential	X											
RBC count	X											
Platelet count	X											
Biochemistry assessment												
Renal Profile (Sodium, Potassium, Creatinine, Urea, eGFR, blood urea nitrogen)	X											
Calcium (bone profile)	X											
Uric acid	X											
Lactate dehydrogenase	X											
Chloride	X											
Bicarbonate	X											
Glucose	X											
Globulin, AST)	X											
Phosphorous	X											
DTP3												
IMP administration	X	X	X	X	X	X	X	X	X	X	X	X
PK												
4ml blood sample												
MULTIPLE MYELOMA PATIENTS:												
Myeloma-specific assessments [h]												
Serum protein electrophoresis (SPEP)	X											
Paraprotein quantification	X											
Serum immunofixation												
Serum immunoglobulin levels												
Serum free light chains (sFLC)	X											
24-hour urine sample for urine proteins and urine immunofixation [e]	X											
FDG-PET/CT whole body MRI, or whole body low-dose CT (unless performed within 8 weeks of treatment starting)												
Bone marrow aspirate and biopsy for local determination of plasma cell count												
Beta-2 microglobulin level												
MM - PD, lab and genetic assessments												
Bone marrow 10mL aspirate												
50ml blood sample												
DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS:												
DLBCL specific assessments [h]												
FDG-PET/CT [j]	X[j]											
Bone marrow aspirate and biopsy [for histological evaluation of DLBCL involvement] [k]												
PD, lab and genetic assessments												
Tumour sample (where accessible)												
50ml blood sample												

	EXPANSION STAGE													
		CYCLE 1												
	Within 28 days prior to first dose	Week 1 Day 1	Week 1 Day 2	Week 1 Day 3	Week 1 Day 5	Week 2 Day 1	Week 2 Day 3	Week 2 Day 5	Week 3 Day 1	Week 3 Day 2	Week 3 Day 3	Week 3 Day 5	Week 4 Day 1	Week 4 Day 3	Week 4 Day 5
		Dose 1	N/A	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	N/A	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12
Initial tests															
Written informed consent	X														
Medical history	X														
Disease specific history (MM/DLBCL)	X														
ECOG Performance Status	X														
Adverse Events		X		X	X	X	X	X	X		X	X	X	X	X
Concomitant medications	X	X		X	X	X	X	X	X		X	X	X	X	X
Physical examination (as per local clinical standards and as considered adequate by the PI)	X														
Height	X														
Weight	X[m]	X[m]			X[m]				X[m]				X[m]		
Blood pressure	X	X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]		X[e]	X[e]	X[e]	X[e]	X[e]
Pulse rate	X	X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]		X[e]	X[e]	X[e]	X[e]	X[e]
Respiratory Rate	X														
12-lead ECG	X	X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]		X[e]	X[e]	X[e]	X[e]	X[e]
Urinalsyis	X	X				X			X				X		
Calculated creatinine clearance	X														
Pregnancy serum (where appropriate)[i]	X														
PT and APTT (coagulation testing)	X														
Full Blood Count (Haematology)															
Haemoglobin	X	X				X			X				X		
Hematocrit	X	X				X			X				X		
WBC count with complete manual or automated differential	X	X				X			X				X		
RBC count	X	X				X			X				X		
Platelet count	X	X				X			X				X		
Biochemistry assessment															
Renal Profile (Sodium, Potassium, Creatinine, Urea, eGFR, blood urea nitrogen)	X	X				X			X				X		
Calcium (bone profile)	X	X				X			X				X		
Uric acid	X	X				X			X				X		
Lactate dehydrogenase	X	X				X			X				X		
Chloride	X	X				X			X				X		
Bicarbonate	X	X				X			X				X		
Glucose	X	X				X			X				X		
LFT (ALT, ALP, Total Bilirubin, Albumin, Total protein, Globulin, AST)	X	X				X			X				X		
Phosphorous	X	X				X			X				X		
DTP3															
IMP administration		X		X	X	X	X	X	X		X	X	X	X	X
PK															
4ml blood sample		X[e]	X[e]	X[e]	X[b]										
MULTIPLE MYELOMA PATIENTS:															
MM specific assessments[g]															
Serum protein electrophoresis (SPEP)	X														
Paraprotein quantification	X														
Serum immunofixation	X														
Serum immunoglobulin levels	X														
Serum free light chains (sFLC)	X														
24-hour urine sample for urine proteins and urine immunofixation[f]	X														
FDG-PET/CT, whole body MRI, or whole body low-dose CT (unless performed within 8 weeks of treatment starting)	X[j]														
Bone marrow aspirate and biopsy for local determination of plasma cell count	X														
Beta-2 microglobulin level	X														
MM - PD, lab and genetic assessments															
Bone marrow 10mL aspirate	X									X[c]					
50ml blood sample	X									X[c]					
DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS:															
DLBCL specific assessments[g]															
FDG-PET/CT (unless performed within 4 weeks of treatment starting)	X														
Bone marrow aspirate and biopsy [for histological evaluation of DLBCL involvement]	X														
DLBCL - PD, lab and genetic assessments															
Tumour sample (where accessbile)	X									X[c]					
50ml blood sample[c]	X									X[c]					

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	EXPANSION STAGE											
	CYCLE 2											
	Week 1 Day 1 Dose 1	Week 1 Day 3 Dose 2	Week 1 Day 5 Dose 3	Week 2 Day 1 Dose 4	Week 2 Day 3 Dose 5	Week 2 Day 5 Dose 6	Week 3 Day 1 Dose 7	Week 3 Day 3 Dose 8	Week 3 Day 5 Dose 9	Week 4 Day 1 Dose	Week 4 Day 3 Dose	Week 4 Day 5 Dose
Initial tests												
Written informed consent												
Medical history												
Disease specific history (MM/DLBCL)												
Adverse Events	×	×	×	×	×	×	×	×	×	×	×	×
Concomitant medications	×	×	×	×	×	×	×	×	×	×	×	×
Physical examination (as per local clinical standards and as considered adequate by the PI)												
Height												
Weight	×[a]			×[a]			×[a]			×[a]		
Blood pressure	×[a]	×[a]	×[a]	×[a]			×[a]			×[a]		
Pulse rate	×[a]	×[a]	×[a]	×[a]			×[a]			×[a]		
Respiratory Rate												
12-lead ECG	×[a]	×[a]	×[a]	×[a]			×[a]			×[a]		
Urinalysis	×						×					
Calculated creatinine clearance												
Pregnancy serum (where appropriate)[i]	×											
PT and APTT (coagulation testing)												
Full Blood Count (Haematology)												
Haemoglobin	×						×					
Hematocrit	×						×					
WBC count with complete manual or automated differential	×						×					
RBC count	×						×					
Platelet count	×						×					
Biochemistry assessment												
Renal Profile (Sodium, Potassium, Creatinine, Urea, eGFR, blood urea nitrogen)	×						×					
Calcium (bone profile)	×						×					
Uric acid	×						×					
Lactate dehydrogenase	×						×					
Chloride	×						×					
Bicarbonate	×						×					
Glucose	×						×					
Globulin, AST)	×						×					
Phosphorous	×						×					
DTP3												
IMP administration	×	×	×	×	×	×	×	×	×	×	×	×
PK												
4ml blood sample												
MULTIPLE MYELOMA PATIENTS:												
MM specific assessments [j]												
Serum protein electrophoresis (SPEP)	×											
Paraprotein quantification	×											
Serum immunofixation												
Serum immunoglobulin levels												
Serum free light chains (sFLC)	×											
24-hour urine sample for urine proteins and urine immunofixation [k]	×											
FDG-PET/CT whole body MRI, or whole body low-dose CT (unless performed within 8 weeks of treatment starting)												
Bone marrow aspirate and biopsy for local determination of plasma cell count												
Beta-2 microglobulin level												
MM - PD, lab and genetic assessments												
Bone marrow 10mL aspirate												
50ml blood sample												
DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS:												
DLBCL specific assessments [j]												
FDG PET/CT[i]												
Bone marrow aspirate and biopsy [for histological evaluation of DLBCL involvement] [k]												
DLBCL - PD, lab and genetic assessments												
Tumour sample (where accessbile)												
50ml blood sample												

EXPANSION STAGE												
	CYCLE 3 & ONWARDS											
	Week 1 Day 1 Dose 1	Week 1 Day 3 Dose 2	Week 1 Day 5 Dose 3	Week 2 Day 1 Dose 4	Week 2 Day 3 Dose 5	Week 2 Day 5 Dose 6	Week 3 Day 1 Dose 7	Week 3 Day 3 Dose 8	Week 3 Day 5 Dose 9	Week 4 Day 1 Dose	Week 4 Day 3 Dose	Week 4 Day 5 Dose
Initial tests												
Written informed consent												
Medical history												
Disease specific history (MM/DLBCL)												
Adverse Events	×	×	×	×	×	×	×	×	×	×	×	×
Concomitant medications	×	×	×	×	×	×	×	×	×	×	×	×
Physical examination (as per local clinical standards and as considered adequate by the PI)												
Height												
Weight	×*			×*			×*			×*		
Blood pressure	×*			×*			×*			×*		
Pulse rate	×*			×*			×*			×*		
Respiratory Rate												
12-lead ECG	×*			×*			×*			×*		
Urinalysis	×											
Calculated creatinine clearance												
Pregnancy serum (where appropriate) [i]	×											
PT and APTT (coagulation testing)												
Full Blood Count (Haematology)												
Haemoglobin	×											
Hematocrit	×											
WBC count with complete manual or automated differential	×											
RBC count	×											
Platelet count	×											
Biochemistry assessment												
Renal Profile (Sodium, Potassium, Creatinine, Urea, eGFR, blood urea nitrogen)	×											
Calcium (bone profile)	×											
Uric acid	×											
Lactate dehydrogenase	×											
Chloride	×											
Bicarbonate	×											
Glucose	×											
Globulin, AST)	×											
Phosphorous	×											
DTP3												
IMP administration	×	×	×	×	×	×	×	×	×	×	×	×
PK												
4ml blood sample												
MULTIPLE MYELOMA PATIENTS:												
MM specific assessments [j]												
Serum protein electrophoresis (SPEP)	×											
Paraprotein quantification	×											
Serum immunofixation												
Serum immunoglobulin levels												
Serum free light chains (sFLC)	×											
24-hour urine sample for urine proteins and urine immunofixation [k]	×											
FDG-PET/CT whole body MRI, or whole body low-dose CT (unless performed within 8 weeks of treatment starting)												
Bone marrow aspirate and biopsy for local determination of plasma cell count												
Beta-2 microglobulin level												
MM - PD, lab and genetic assessments												
Bone marrow 10mL aspirate												
50ml blood sample												
DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS:												
DLBCL specific assessments [j]												
FDG PET/CT	×[i]											
Bone marrow aspirate and biopsy [for histological evaluation of DLBCL involvement] [k]												
DLBCL - PD, lab and genetic assessments												
Tumour sample (where accessbile)												
50ml blood sample												

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End of Treatment Visit	
	End of Study Visit
Initial tests	
Survival Status	X[k]
Written informed consent	
Medical history	
Disease specific history (MM/DLBCL)	
ECOG Performance Status	X
Adverse Events	X
Concomitant medications	X
Physical examination- including ECOG performance status (as per local clinical standards and as considered adequate by the PI)	X
Height and weight	
Blood pressure	X
Pulse rate	X
Respiratory Rate	
12-lead ECG	X
Urinalsyis	
Calculated creatinine clearance	
Pregnancy serum (where appropriate)[i]	X
PT and APTT (coagulation testing)	
Full Blood Count (Haematology)	
Haemoglobin	
Hematocrit	
WBC count with complete manual or automated differential	
RBC count	
Platelet count	
Biochemistry assessment	
Renal Profile (Sodium, Potassium, Creatinine, Urea, eGFR, blood urea nitrogen)	
Calcium (bone profile)	
Uric acid	
Lactate dehydrogenase	
Chloride	
Bicarbonate	
Glucose	
LFT (ALT, ALP, Total Bilirubin, Albumin, Total protein, Globulin, AST)	
Phosphorous	
PK	
4ml blood sample	
MULTIPLE MYELOMA PATIENTS:	
MM specific assessments	
Serum protein electrophoresis (SPEP)	
Paraprotein quantification	
Serum immunoglobulin levels	
Serum free light chains (sFLC)	
Plasmacytoma evaluation	
Beta-2 microglobulin level	

Keys	
a	**Hospitalised patients** will undergo the following sampling: pre-infusion, 5min, 0.25hr, 0.5hrs, 1hr, 2hr, 4hr, 8hr, 12hr, 16hr, and 24hr **Non-hospitalised patients** will undergo the following sampling: pre-infusion, 5min, 0.25hr, 0.5hrs, 1hr, 2hr and 4hr (post-infusion) For PK samples taken during the first hour of sampling, these samples need to be taken as precisely as possible at the specified time points idealy within +/- 2 minutes. For samples taken after the first hour, there can be a small window of +/- 5 minutes, for samples taken at 12 hours and later a window of 30 minutes is allowed. The exact time of bleeding will anyway be registered on the log.
b	Pre infusion, 0.5hr, 1hr,2hr and 4hr (post-infusion)
c	These samples will be collected 24 hours (range 18-36 hours) after completion of administration of the FOURTH dose of DTP3. Further samples will be collected if a complete response is suspected or clinically required as determined by the Investigator
d	Patients receiving DTP3 after cycle 3 will continue with the assessments scheduled as per cycle 3
e	**Dose Escalation Stage**: *Week 1 and 2* : During Cycle 1, BP, pulse rate and 12 lead ECG will be carried out 15 min before and 30 mins, 60 min and 120 min after end of each DTP3 infusion (+/- 5mins). *Week 3 and 4:* During Cycle 1, BP, pulse rate and 12 lead ECG will be carried out 15 min before and 30 mins after end of each DTP3 infusion (+/- 5mins). *Cycle 2-onwards* : BP, pulse rate and 12 lead ECG will be carried out 15 min before and 30 mins after end of each DTP3 infusion (+/- 5mins). **Cohort Expansion Stage**: *Week 1* : During Cycle 1, BP, pulse rate and 12 lead ECG will be carried out 15 min before and 30 mins,after end of each DTP3 infusion. *Week 2 onwards* : BP, pulse rate and 12 lead ECG will be carried out before the first dose of DTP3 at the beginning of week 2 onwards (eg. before dose 4,7,10 etc)
f	Only to be done on a monthly basis in patients with detectable urinary M protein at screening
g	Pre-infusion
h	Bone marrow aspirate and biopsy required if radiological complete response
i	Serum pregnancy test (where appropriate) at beginning of each cycle of DTP3 and then monthly for six months after cessation of DTP3 therapy.
j	To continue 8 weekly for evaluation as long as participating
k	Where this is no Disease Progression when ceasing DTP3 treatment, survival status to continue being recorded for a period of six months after the last patient has been recruited into the study. Via clinic team if under their care, or six weekly via family member.
l	Possible tests pending patient outcome of disease progression or complete resolution and local institutional practice: If at any point, a **complete reponse** is suspected in a patient, they will undergo: **MM:** **1. Two independent measurements** (according to normal institutional practice) confirming: -negative immunofixation serum -negative immunofixation urine **2. Bone marrow aspirate and biopsy** (if above tests are consistent with definition of complete response) **DLBCL:** A bone marrow aspirate and biopsy is required for confirmation of radiological complete response. If at any point, there is clinical suspicion of **disease progression**: **MM:** This can be determined by measurement of any relevant disease parameter, including radiological imaging and/or bone marrow plasma cell percentage, but should be confirmed by two independent measurements, according to normal institutional practice. **DLBCL:** FDG-PET/CT imaging will be performed every 8 WEEKS after the first dose of DTP3, unless clinically indicated at an earlier time point (e.g. if there is clinical suspicion of disease progression). Response assessment at each FDG-PET/CT timepoint will be made according to the Lugano 2014 criteria (Appendix B of protocol).
m	The most recently available weight should be used when calculating the amount of DTP3. The weight used to calculate the dose of DTP3 can have been taken up to 10 days prior to administration of the first dose of each cycle)